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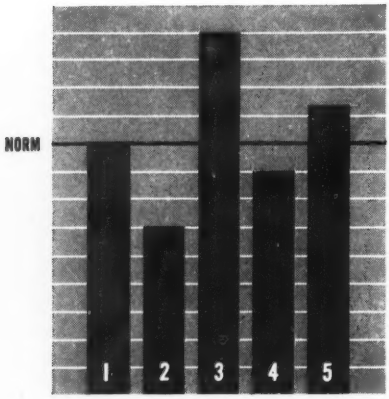

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VOLUME 8 SEPTEMBER, 1948 NUMBER 9
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PUBLICATION AGREEMENT WITH THE AMERICAN GOITER ASSOCIATION

A PUBLICATION agreement has been completed between the Association for the Study of Internal Secretions and the American Goiter Association (formerly the American Association for the Study of Goiter). It was approved at the annual meeting of the Association for the Study of Internal Secretions in Chicago in June and at the annual meeting of the American Goiter Association in Toronto in May.

According to this agreement, all articles presented at the annual meeting of the American Goiter Association will be submitted to the JOURNAL OF CLINICAL ENDOCRINOLOGY. The decision of the Editorial Board and of the Editorial Office will be final concerning publication in this JOURNAL. This means that the articles presented at the annual meeting of the American Goiter Association will be subjected to the same editorial review that is given to articles presented at the annual meeting of the Association for the Study of Internal Secretions and to all other articles submitted to the JOURNAL for publication.

All articles presented at the annual meeting of the American Goiter Association will be published in their *Transactions* regardless of whether or not they are published in the JOURNAL OF CLINICAL ENDOCRINOLOGY. The *Transactions* will be published by Charles C Thomas of Springfield, Illinois, who also publishes the JOURNAL.

The decision of the American Goiter Association to enter into a publication agreement with our Association represents a very definite forward step in the field of clinical endocrinology. It provides a common publication medium for two outstanding endocrine groups. It is hoped that similar publication agreements may be completed with other endocrine organizations.

It is the desire of most members of our Association and of our officers and of our Editorial Board to broaden the scope of the JOURNAL OF CLINICAL ENDOCRINOLOGY. It is felt that it should include articles in all fields of clinical endocrinology and in the field of metabolism.

It is the opinion of our Publications Committee and of the Editorial Office that some suitable recognition should be given to the American Goiter Association to let them know how enthusiastic we are about the completion of this publication agreement. For this reason, the present issue of the JOURNAL has been designated as an "American Goiter Association number" and only articles presented at the annual meeting of the American Goiter Association are included in it. It was not possible to include all of the articles in the September issue. The remaining articles will appear in future issues and their publication should be completed by December or January.

WILLARD O. THOMPSON, M.D

"A bound volume of all articles appearing in this issue of THE JOURNAL OF CLINICAL ENDOCRINOLOGY and subsequent articles pertaining to transactions of the American Goiter Association is being published by the Charles C Thomas Publishing Company and will be available in the early part of 1949."

THE BIOLOGIC EFFECT OF IRRADIATION BY RADIOACTIVE IODINE*†

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TRACER doses of radioactive isotopes have been used in biology and medicine with the assumption that their radiation does not change the physiology under investigation. However, there have been few studies made to establish this assumption as fact.

Radioactive iodine has now been widely used for about ten years in the study of thyroid physiology and iodine metabolism. In order to interpret correctly the results of these studies, knowledge of any possible radiation effects of radioactive iodine tracer doses is necessary.

We have undertaken studies with radioactive iodine (I^{131}) in doses which have been used as "tracers" with two main objectives:

1) to determine the minimal amount of radioactive iodine which may interfere with the normal function of the thyroid and
2) to study the effects of irradiation by radioactive iodine on various known functions of the thyroid.

The purpose of this paper is to report the radiation effect of I^{131} on the thyroid in respect to:

1) collection of radioactive iodine
2) capacity for growth
3) capacity to collect iodine (from food and water)
4) capacity to respond to thiouracil
5) capacity to respond to thyrotropic hormone.

METHODS AND MATERIALS

Since I^{131} (8-day iodine) has been the most widely used isotope of iodine in tracer studies, we chose it for our investigation. In most of the tracer studies reported in the literature, it is very difficult or often impossible to evaluate what doses of radioactive iodine have been used. Two important reasons for these discrepancies are that doses are not given in absolute

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† Aided by a grant-in-aid from the American Cancer Society as recommended by the Committee on Growth.

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units (curie or rutherford), or when given in absolute units there is still great variation among various laboratories in the standardization of the isotope. Our standardization in absolute units has been done by comparing the gamma radiation from I^{131} and that from standard radium, using a platinum screen cathode Geiger-Mueller counter with known efficiency for various gamma ray energies. It might be pointed out that our microcurie is among the smallest in the country and that, therefore, the radiation effects we have produced with our doses may be still more pronounced in other laboratories where their microcurie of iodine gives off more radiation. At the present time, it does not seem worth while to try to resolve the differences in the absolute standardization of I^{131}, since Metzger and Deutsch (1) have now found that the decay of I^{131} is much more complicated than earlier supposed, and the simple disintegration scheme Downing, Deutsch and Roberts (2) had determined is no longer valid.

Experimental procedure: In all experiments five-day old cockerels were injected with 0.5 unit of thyrotropic hormone for three consecutive days. Twenty-four hours after the last injection three groups were injected subcutaneously with I^{131} (containing 0.1 microgram sodium iodide as a carrier) in doses of 1, 10 and 50 microcuries, respectively. A fourth group received no radioactive iodine and was used as a control.

RESULTS

The effect on the thyroid collection of I^{131} with varying doses of the isotope

In our first experiments we were trying to determine any possible effect of radioactive iodine on the physiology of the thyroid by measuring the percentage uptake of the isotope in the thyroid at various intervals.

Figure 1 and Table 1 show the result of such an experiment. 0.5 μc, 1 μc,

TABLE 1. THE EFFECT ON THE THYROID COLLECTION OF I^{131} OVER A PERIOD OF 48 HOURS, USING VARYING DOSES OF THE ISOTOPE

Dose of I^{131} (microcuries)	Time interval after injection of I^{131}				
	4 hours	12 hours	24 hours	36 hours	48 hours
0.5	8.08 ±0.81*	10.40 ±0.93	12.25 ±0.90	9.80 ±0.86	8.42 ±0.67
1.0	8.35 ±0.70	10.70 ±0.74	12.94 ±1.03	10.23 ±0.84	8.28 ±0.79
10.0	8.64 ±0.77	10.14 ±0.78	12.00 ±0.94	10.52 ±0.69	7.95 ±0.59
50.0	8.95 ±0.67	10.28 ±0.84	12.45 ±0.88	10.37 ±0.76	7.22 ±0.61

* Each value represents the average percentage of 15 animals. The means are given with their standard errors.

10 μc and 50 μc of I^{131} were administered. The chicks were sacrificed at intervals during a 48-hour period as indicated in Figure 1. Each point on the curves represents the average of the uptake in 15 chicks. These 48-hour collection curves demonstrate a consistent similarity in uptake for various doses of I^{131}. There is no statistical difference demonstrable at any point of the uptake curves. As long as these collection curves superimpose, one can feel certain that physiologic processes have not been altered. When the curves begin to deviate, however, one can be likewise convinced that the physiologic processes under study have been changed.

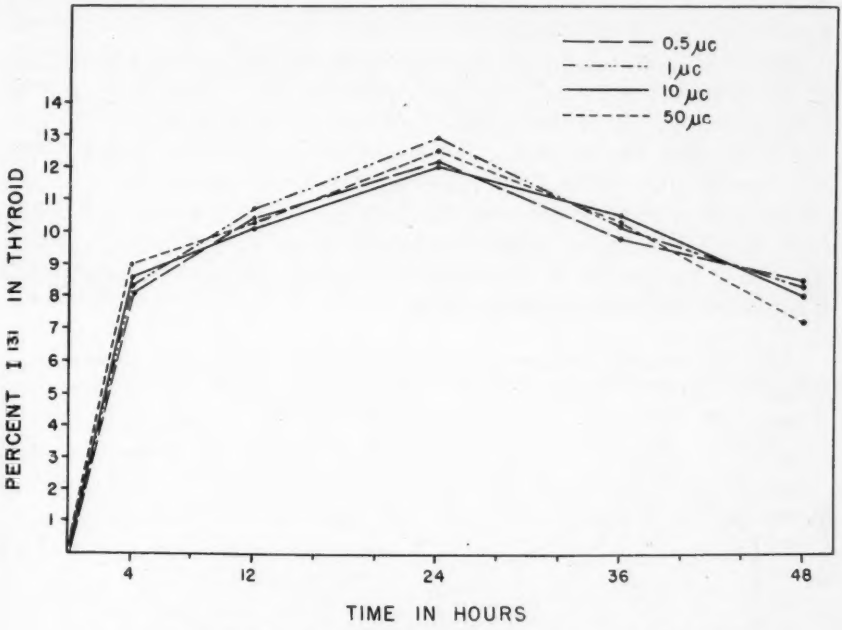

FIG. 1. The effect on the thyroid collection of I^{131} over a period of 48 hours, using varying doses of the isotope.

Figure 2 and Table 2 demonstrate the result of a similar experiment which was extended over 168 hours. These curves superimpose well for the first 96 hours. The differences between the curves are due to inaccuracies in the experimental technique and biologic variation among the animals. They are not statistically significant. At the 144 and 168 hour intervals, however, there is a smaller concentration in the 50 μc group than in the 1 μc group. Comparison between the 10 μc group and the 1 μc group does not reveal any statistical difference. Thus it is apparent that the thyroid cannot

TABLE 2. THE EFFECT ON THE THYROID COLLECTION OF I^{131} OVER A PERIOD OF 168 HOURS, USING VARYING DOSES OF THE ISOTOPE

Dose of I^{131} (microcuries)	Time interval after injection of I^{131}					
	4 hours	24 hours	48 hours	96 hours	144 hours	168 hours
1	10.02±1.07*	13.59±1.82	10.27±1.23	7.08±1.00	5.66±1.26	5.20±0.90
10	8.86±1.13	13.19±1.03	8.32±1.11	6.52±1.00	3.16±0.44	2.72±0.52
50	10.20±1.36	12.53±0.97	8.82±1.29	5.36±0.78	2.10±0.27	1.48±0.38

* Each value represents the average percentage of 15 animals. The means are given with their standard errors.

retain over any extended period of time a large dose of radioactive iodine as well as it can a smaller dose.

When radioactive iodide is taken up by the thyroid it is rapidly utilized in the synthesis of thyroid hormone. One can feel certain that after 96 hours practically all of the radioactive iodine in the thyroid is in the hormonal fraction. The decreased concentration of radioactive iodine in the 50 μc group after 144 and 168 hours does therefore indicate an increased release of thyroid hormone, which is likely to be caused by the irradiation from radioactive iodine. This phenomenon must be taken into account when large doses of I^{131} are used in tracer studies and when the experiment is extended over a long period of time.

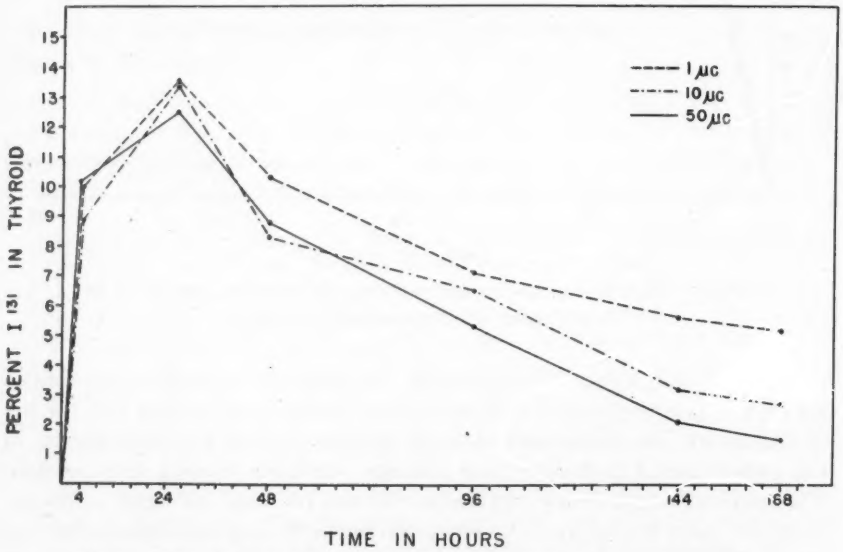

FIG. 2. The effect on the thyroid collection of I^{131} over a period of 168 hours, using varying doses of the isotope.

These collection curves also give us an opportunity to calculate approximately the total doses of radiation to which these thyroids are exposed. In the use of x-rays the radiation doses are usually expressed in roentgens. The x-rays produce high speed secondary electrons in the tissue and the radiation effects of x-rays are due to the interaction of these electrons with the tissue. The beta rays from a radioactive isotope are also high speed electrons. One can therefore assume that the beta rays and x-rays produce similar effects on tissues. Beta rays have a maximum range of only a few millimeters in tissue and the radiation is almost exclusively limited to the tissue containing the radioactive isotope. Since by definition the roentgen unit is confined to gamma and x-radiation, one should use the comparable unit roentgen-equivalent-physical (rep) when the tissue ionization is caused by any other primary radiation (e.g. beta rays, protons, alpha rays, neutrons (Evans (3)). It can be demonstrated that 1 μc of 8-day iodine per mg. of tissue delivers 8.5 rep per minute (Chapman and Evans (4)). In their calculation the radiation due to the gamma rays from I^{131} was neglected because of the very small absorption of these rays in the thyroid.

The estimation of the total dose of radiation to the thyroid was made according to the method given by Chapman and Evans (4). Table 3 shows the results of such an estimation for a dose of 1 μc. The total radiation dose

TABLE 3. ESTIMATION OF RADIATION TISSUE DOSE FROM 1 MICROCURIE OF I^{131}

Time interval	Fraction of administered I^{131} retained in gland	Fraction of original 8-day radioactivity remaining			Dose in interval $D = 35200 \times R \times (F_1 - F_2)$	Total dose in tissue (roentgen-equivalent-physical) due to 8-day iodine
		At beginning of time interval	At end of time interval			
t_1 and t_2	R	F_1	F_2	$F_1 - F_2$		
0–4 hr.	0.042	1.000	0.986	0.014	21	21
4–12 hr.	0.095	0.986	0.956	0.030	100	121
12–24 hr.	0.118	0.956	0.914	0.042	174	295
24–36 hr.	0.116	0.914	0.874	0.040	163	458
36–48 hr.	0.093	0.874	0.836	0.038	125	585
48–96 hr.	0.087	0.836	0.698	0.138	423	1006
96–144 hr.	0.064	0.698	0.588	0.110	248	1254
144–168 hr.	0.054	0.588	0.543	0.045	86	1340
168–480 hr.*	0.026*	0.543	0.175	0.368	337	1677

* Estimated from the slope of the curve.

from 1 μc of I^{131} was quite high, about 1,700 rep. For 10 μc the total dose was about 13,000 rep and for 50 μc about 60,000 rep. It should be pointed out, however, that these figures are only approximate. Thus in terms of roentgen-equivalent-physical the amount of radiation to the thyroid is large. However, this radiation emanates from doses of I^{131} often used in tracer experiments.

Effect of I^{131} on growth of thyroid and on thyroid iodine

Four groups of chicks were given I^{131} in doses of 0 μc, 1μc, 10 μc and 50 μc and sacrificed after sixteen and twenty-four days.

In this experiment we were able to demonstrate the effect of I^{131} on thyroid growth as indicated by thyroid weight and thyroid iodine concentration. The columns in Figure 3 represent the average result from 20 animals. In the 10 μc and 50 μc groups there is a definite inhibition of the normal growth both after sixteen and twenty-four days. The difference between the 1 μc group and the nonradiated controls is not statistically

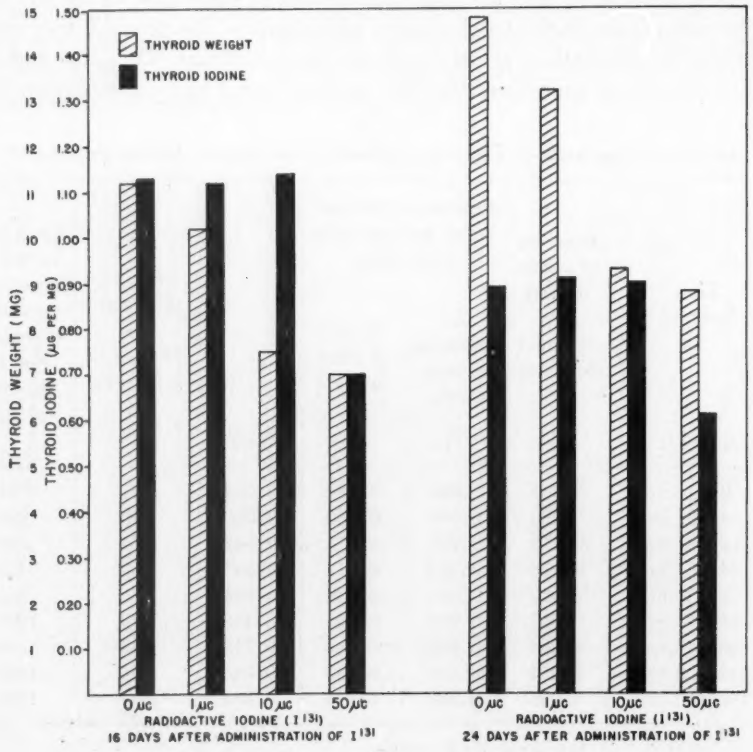

FIG. 3. The effect of I^{131} on thyroid growth and thyroid iodine.

significant. It can also be seen from Figure 3 that the radiation has inhibited to some degree the ability of the thyroids in the 50 μc group to concentrate iodine from food and water. It might be pointed out that there is a normal concentration of iodine in the 10 μc group. It should also be mentioned that there was no demonstrable difference in body weight among the different groups. This experiment, which has been confirmed by several other similar ones (Fig. 4 and Fig. 5) thus demonstrates that these two functions of the thyroid—to grow and to concentrate iodine—have a different sensitivity to radiation. Growth appears to be more sensitive to damage from radiation

Response to thiouracil after irradiation with I^{131}

Four groups of chicks were given I^{131} in doses of 0 μc, 1 μc, 10 μc and 50 μc. Sixteen and twenty-eight days later half of the chicks in each group were given 0.1 per cent thiouracil in drinking water for ten days and then sacrificed.

Figure 4 shows the results of this experiment. The radiation effects on thyroid weights, discussed earlier, were confirmed by the control thyroids. In the animals which received thiouracil and were sacrificed twenty-six

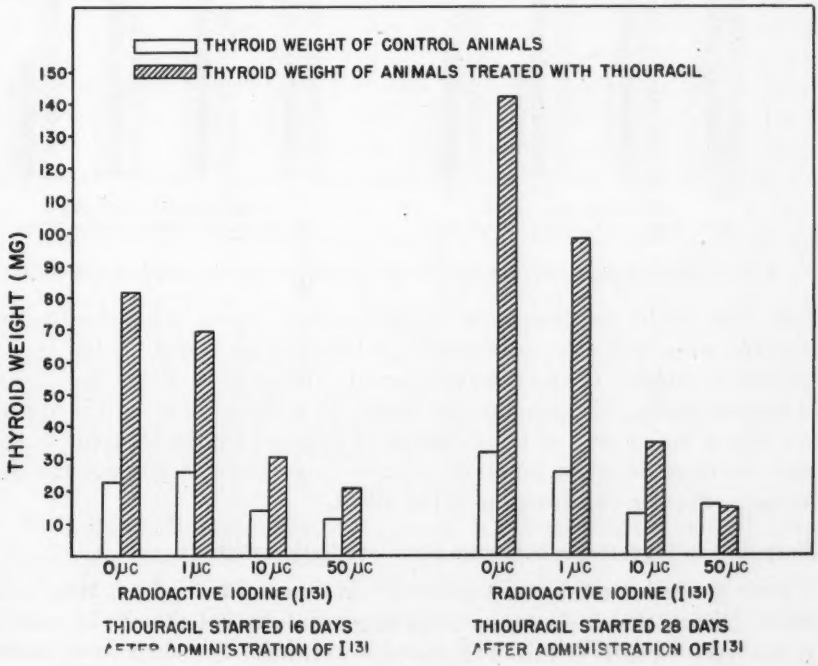

FIG. 4. The thyroid response to thiouracil after irradiation with I^{131}.

days after the I^{131} was administered there was in all groups, controls as well as irradiated, an increase in thyroid weight. In the animals sacrificed thirty-eight days after administration of I^{131} there was no longer any increase in thyroid weight in the 50 μc group. The 1 μc and 10 μc groups still responded to thiouracil, though it appears that the response was not as good as in the nonradiated controls. This experiment showed at twenty-six

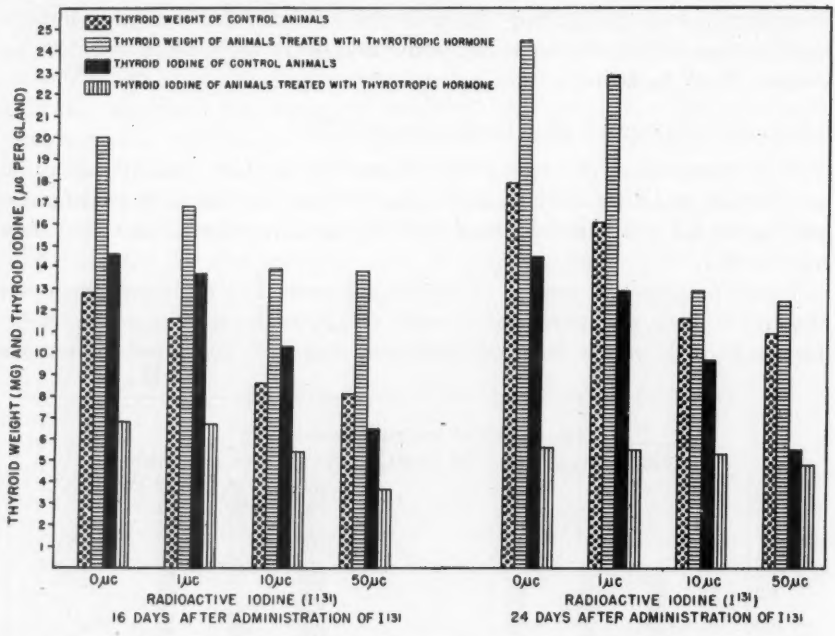
THYROID WEIGHT OF CONTROL ANIMALS
THYROID WEIGHT OF ANIMALS TREATED WITH THYROTROPIC HORMONE
THYROID IODINE OF CONTROL ANIMALS
THYROID IODINE OF ANIMALS TREATED WITH THYROTROPIC HORMONE
THYROID WEIGHT (MG) AND THYROID IODINE (μg PER GLAND)
0μc
1μc
10μc
50μc
RADIOACTIVE IODINE (I131)
16 DAYS AFTER ADMINISTRATION OF I131
RADIOACTIVE IODINE (I131)
24 DAYS AFTER ADMINISTRATION OF I131

FIG. 5. The thyroid response to thyrotropic hormone after irradiation with I^{131}.

days that despite the decrease in thyroid weight caused by irradiation, the thyroids were still able to respond to thiouracil as demonstrated by an increase in weight. It also demonstrates the importance of the time factor in producing the radiation damage. From the collection curves it is apparent that a major part of the radiation is received by the thyroids in the first few days. It takes, however, a much longer time to produce the full biologic effect on the function of the gland.

Response to thyrotropic hormone after irradiation with I^{131}

Four groups of chicks were given I^{131} in doses of 0 μc, 1 μc, 10 μc and 50 μc. During the three days preceding sacrifice half of the chicks in each group received daily $\frac{1}{2}$ unit of thyrotropic hormone. The chicks were sacrificed after sixteen and twenty-four days.

The thyroids were weighed and analyzed for iodine content. In the chicks which were sacrificed sixteen days after the administration of I^{131} there was observed in all groups an increase in thyroid weight and loss of thyroid iodine. The response in the irradiated thyroids was comparable to that of the nonradiated controls. However, in the chicks which were sacrificed twenty-four days after the administration of radioactive iodine the response to thyrotropic hormone was entirely different. The group which received 1 μc responded typically to thyrotropic hormone as did the nonradiated controls. In the 10 μc group the thyroids did not increase in weight but there was a normal loss of iodine. In the 50 μc group, however, there was observed no increase in thyroid weight and the loss of thyroid iodine was very small, if any. When the same experiment was repeated, there was observed some loss of iodine in the 50 μc group, though this was a much smaller loss than in the other groups. Figure 5 also clearly demonstrates the earlier discussed effect of irradiation on the growth of the thyroids as well as on their capacity to concentrate iodine. It should also be mentioned that in the groups sacrificed sixteen days after the administration of I^{131}, despite the fact that the radiation had inhibited the thyroids' normal growth and iodine concentrating mechanism, the response to thyrotropic hormone was good in all radiated groups as demonstrated by an increase in thyroid weight and a loss of thyroid iodine, comparable to the response in the untreated controls. From the physiologic standpoint it is most interesting that we have been able by means of irradiation with radioactive iodine to separate two known actions of thyrotropic hormone. These results suggest that the thyrotropic hormone acts on the thyroid through at least two different mechanisms, and that these two actions have a different sensitivity to radiation.

These reported experiments represent a beginning in the study of the radiation effects of radioactive iodine. We have thus far investigated radiation effects on various known functions of the thyroid. We have been able to demonstrate very clearly that some of these functions differ in their sensitivity to radioactive iodine. We have not yet studied the mechanism through which the radiation acts on the thyroid cell but we hope that our further studies will elucidate this problem and also throw some light on radiation mechanisms in living cells generally.

SUMMARY

We have studied the effect of radioactive iodine (I^{131}) on various functions of the thyroid in cockerels.

Determination of thyroid collection curves for 0.5 μc, 1 μc, 10 μc and 50 μc of I^{131} demonstrated that during the first 96 hours no physiologic change took place in the thyroid at any dose level. The earliest radiation effect was observed in the 50 μc group 144 hours after administrating the

isotope. This indicated that the thyroid does not retain a large dose of I^{131} as well as it does a smaller one for any extended period. The total radiation dose to the thyroids has been estimated.

The effect of I^{131} on the thyroid's growth and iodine content was studied. Thyroids of chicks which had received 1 μc of I^{131} did not change in growth or iodine concentration. In animals which received 10 μc and 50 μc the normal growth of the thyroid was significantly inhibited. Iodine concentration was not altered in the animals which received 10 μc, but there was a significant decrease in concentration of thyroid iodine in the 50 μc group.

We demonstrated the effect of I^{131} on the thyroid's ability to respond to thiouracil. The animals received thiouracil for the ten-day period before sacrifice. All irradiated animals responded to thiouracil as measured by increase in thyroid weight twenty-six days after administering I^{131}. However, thirty-eight days after they received I^{131} there was no longer any response to thiouracil in the 50 μc group and in the 10 μc groups the response was not as marked as in the nonradiated controls.

An investigation of the effect of I^{131} on the thyroid's response to thyrotropic hormone showed that all irradiated animals responded to thyrotropic hormone as measured by increase in thyroid weight and loss of iodine sixteen days after administering I^{131}. However, at the twenty-four day interval there was demonstrated a dissociation in response to thyrotropic hormone between the 10 μc and 50 μc group. In the 10 μc group a loss of iodine was observed but no increase in thyroid weight. In the 50 μc group there was no effect on thyroid weight and the loss of iodine was minimal.

We have demonstrated that so-called "tracer" doses of I^{131} may alter normal functions of the thyroid and that these functions vary in their sensitivity to irradiation from this isotope

ACKNOWLEDGMENT

Grateful acknowledgment is made to Drs. J. H. Means, R. W. Rawson and R. D. Evans for their helpful suggestions and for the facilities provided in their laboratories for this work; to Miss Priscilla Merrill, Mrs. Charlotte Riddell and Miss Lorraine Kirschner for technical assistance and aid in preparation of the manuscript.

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THE COLLECTION OF RADIOACTIVE IODINE BY THE HUMAN FETAL THYROID*

EARLE M. CHAPMAN, M.D., G. W. CORNER, JR., M.D., DAVID ROBINSON, M.D. AND R. D. EVANS, PH.D.

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THE age at which the human fetal thyroid begins to function has been a matter of speculation for many years. Certain approximate time relations in regard to function have been assigned on the basis of studies such as Gorbman's (1, 2) of the lower forms of animal life. In 1836 Jones (3) was perhaps the first to describe the microscopic structure of the human fetal thyroid. He found that the thyroid was beginning to form differentiated tissue in a fetus of 4½ months. Both Horcicka (4) and Podack (5) late in the nineteenth century observed that typical glandular structure did not appear until the fifth fetal month.

In Cooper's (6) study of the human thyroid at various ages of intrauterine growth, she observed the beginning of follicle formation by the thirteenth week, but no colloid or secretion within the lumina until late in the fourth month of pregnancy. The more differentiated tissue containing colloid seemed to appear at the periphery of the thyroid. Observations by Norris (7) indicated that typical colloid does not appear until the embryo measures 60 mm. (C-R), or is approximately 12 to 13 weeks old.

We are not aware, however, of definitive studies of this problem in human physiology. It occurred to us that the earliest age at which collection of radioactive iodine by the human fetal thyroid could be observed would be an indicator of the age of onset of thyroid function.

METHODS

A cooperative investigation was planned with the pathologists at the Boston Lying-in Hospital and the physicists at the Massachusetts Institute of Technology. Pregnant women with organic disease that endangered their health, were given tracer doses of radioactive iodine from twelve to forty-eight hours before operation. The urinary excretion of radioactivity was measured. At operation the intact fetus was obtained and carefully measured for the approximation of age in weeks. The fetus was then fixed

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* Read before the Annual Meeting of the American Association for the Study of Goiter, Toronto, Canada, May 6, 1948.

TABLE 1. COLLECTION OF RADIOACTIVE IODINE BY THYROIDS OF FETUSES RANGING IN AGE FROM 7 TO 32 WEEKS

Fetus No.	Per cent maternal urinary excretion of I^{131}	Fetal length (millimeters)	Age in weeks	Sex	Histology of the thyroid	Collection of radioactive iodine by the thyroid
1	Hrs. % 0–24 58 24–48 7	19	7		Undifferentiated	0
2	0–24 28 24–48 —	52	11		Undifferentiated	0
3	0–24 61 24–48 1	55	11.5	Male	Undifferentiated	0
4	0–24 24–48	55	11.5	Male	Undifferentiated	0
5	0–24 55 24–48 1	58	12	Male	Undifferentiated	0
6	0–24 59 24–48 3	95	14.5	Male	Undifferentiated	0.08%/Gm.
7	0–24 56 24–48 1	110	16	Male	*Follicles	0.12%/Gm.
8	0–24 18 24–48 3	170	20	Male	Follicles	0.11%/Gm.
9	0–24 56 24–48 6	280	32	Male	Follicles	4.83%/Gm.

* Photomicrograph (*see* Fig. 1).

in formalin and sectioned longitudinally through the midline. Tissues from one half were prepared for microscopic section, while those from the other half were macerated in 5 per cent potassium hydroxide for Geiger counts of radioactivity.

Tissues to be macerated were obtained from three levels: first, from the upper pharynx down to the upper thorax; second, from the upper thorax to the upper abdomen; and third, from the upper to the lower abdomen.

Histologic study of the tissue harboring radioactivity was thus possible by what our Canadian cousins might designate a study of "opposite numbers." Radioautographs were not attempted.

RESULTS

Tissues from 9 fetuses ranging in age from 7 to 32 weeks have been studied in the manner described (Table 1). In those aged 7 to 12 weeks the tissue containing thyroid did not exhibit radioactivity. In those aged from

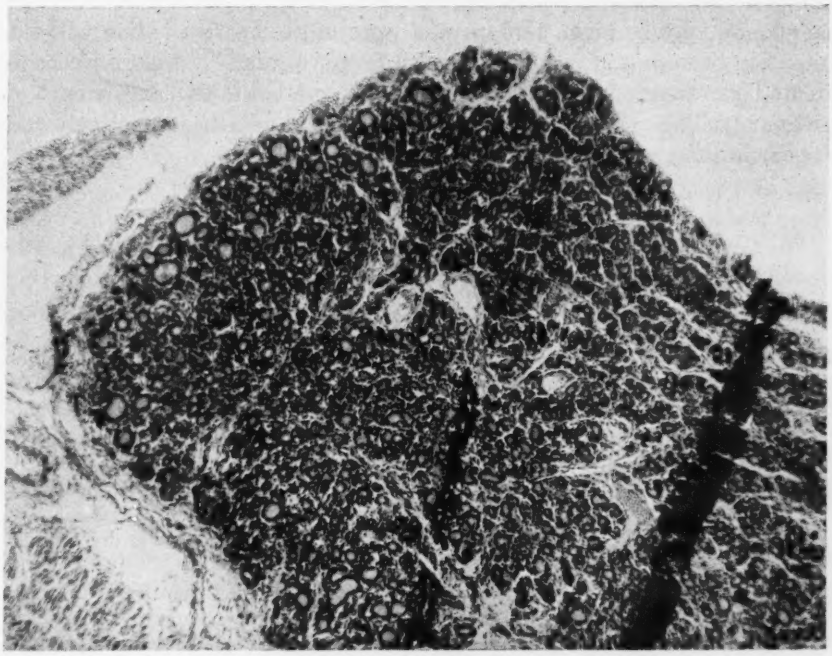

FIG. 1. Section of thyroid from fetus no. 7, aged 16 weeks (Table 1), showing follicle formation with colloid and minimal collection of radioactive iodine.

14 to 32 weeks, the thyroid showed an amount of radioactivity that seemed to increase with succeeding ages in weeks. Other tissues did not contain appreciable amounts of radioactivity, so it seems that iodine has its selective affinity for the thyroid even at this early age.

Histologic studies of the fetal thyroid confirm the previous opinion that the onset of function as measured in this manner is associated with the appearance of definite follicles containing colloid (Fig. 1).

SUMMARY AND CONCLUSIONS

Our studies indicate that the human fetal thyroid does not collect administered radioactive iodine in the first twelve weeks of life and that increasing amounts of radioactive iodine are collected after the fourteenth week. If we assume that radioactive iodine collection and functional activity are synonymous, then by this method we have approximated the age of onset of physiologic activity of the human fetal thyroid.

A practical application of this knowledge lies in the use of radioactive iodine in the treatment of toxic goiter. Women up to the fourth month of pregnancy may be given therapeutic doses of radioactive iodine without retention of such radioactivity by the fetus. Actually, to date, we have treated one woman in the second month and another in the sixth month of pregnancy. Their children are now aged 14 and 18 months respectively and appear healthy and show no signs of myxedema.

ACKNOWLEDGMENT

We are indebted to Hilda Yee and Helen Lockhart for technical assistance in measuring the radioactivity.

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DOSIMETRIC AND PROTECTIVE CONSIDERATIONS FOR RADIOACTIVE IODINE*

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INTRODUCTION

I AM deeply appreciative of the honor done me by your society in asking that I give the guest lecture at your annual meeting. In a very real sense however, the honor is more properly assigned to you. I am here only because you are seeking to discharge your highest duties as physicians by looking for counsel on the hazards of the new, exciting, and largely uncharted regions that are revealed by the application of radioisotopes to medical problems. I am here not as an expert with all the answers, but as a colleague whose prior experience perhaps qualifies me to indicate the areas in which more knowledge is necessary if the patient's best interests are to be protected, and to indicate the reasons for and methods of protecting ourselves and our assistants from the dangers of these new tools.

The problems we shall discuss today are new ones in the sense that the medical profession as a whole has had little reason to concern itself with them. To those of us who have been interested in radiobiology and radiotherapeutics, they are very old and vexing problems. Your interest in radioiodine for therapeutic purposes, unhappily for you and happily for us, means that you inherit the problems of the radiobiologist and radiotherapist, since you will be practicing radiotherapy. Your interest in radioiodine for tracer studies necessitates an interest, if only by exclusion, in radiobiology since it is of importance to demonstrate that the systems which you will study are not affected by their absorption of radiant energy.

The specific problems can be stated simply: What amount of radiation can be given the thyroid gland without producing any detectable effect? What indices of effect should be used? What is the least amount of radiation per gram of thyroid that will return the elevated basal metabolic rate to normal? How much radioiodine must be deposited in each gram of thyroid cancer to kill the neoplastic cells?

DOSIMETRY

The amount of a given agent necessary to produce a given effect is one of the therapeutic interests of all physicians. Two factors are of concern:

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first, to give enough to produce the desired effect; and second, to avoid if possible the toxic or lethal effects of overdosage. These considerations are as valid for the use of radioiodine as for the use of morphine. The fact that toxic effects may be seen after the administration of nontherapeutic amounts of radioiodine is a complicating factor not normally noted in the pharmacology of nonradioactive compounds. The fact that the toxic effects of radioactive compounds, presumably including radioiodine, may be seen many years after the radioactive compound was given also introduces a factor not known to be associated with the use of ordinary drugs. Since the use of radioactive compounds in medicine, even of radioiodine, is in its infancy, and since the amounts of radioactivity necessary to produce a therapeutic effect or to produce a harmful effect are not yet known, it is of importance to record as precisely as possible all pertinent data on the patients now being treated or studied with radioiodine. Failure to do so will prolong the period of uncertainty and may well delay the application of other radioactive compounds to medical problems.

What things should we know? First, the amount given to the patient. Usually the acquisition of this piece of information is not difficult since all that is needed is means for taking an accurately measured sample of the solution to be given and access to a calibrated Geiger-Müller counter. Second, the maximal concentration of radioiodine initially present in the gland. To know this it is necessary to use a counter whose counts per unit time per microcurie I^{131} are known for situations comparable to those in the neck of the patient. Third, the size and weight of the thyroid gland. Obviously this cannot be directly known, but I am told that many physicians can estimate these values within 25 per cent and this at the present time may be sufficient. The accuracy of this figure might be increased by refinement of radiologic techniques. It may be that the thyroid could be radiologically visualized following the injection of oxygen into the neck. Fourth, the effective half-life of I^{131} in the thyroid must be known. This factor is determined by plotting the fall in activity from the thyroid gland against time. If these four factors are known, or estimates of them can be made, it is then possible to correlate microcuries of I^{131} per gram of thyroid with the effect produced.

Initially, it would appear that the dosimetric considerations had been completely satisfied. The good results produced by the use of I^{131} in diseases of the thyroid as well as the toxic properties of therapeutic or tracer amounts are caused by the radiations given off by that element. Hence it can be claimed justly that the calculations of dose should be expressed in terms of the roentgen, the basic unit of radiotherapeutics and radiobiology. If this is done it becomes much easier to estimate the probability of damage from a given exposure to radioiodine, and also to integrate the experience

gained in this field into the general body of radiotherapeutic and radiobiologic knowledge.

Even though the above factors are known, certain assumptions must still be made. At the present time it is necessary to assume uniform distribution of the I^{131} throughout the thyroid, an assumption rarely realized. We also assume that beta ray roentgens have the same biologic action as x-ray roentgens, an assumption that is probably imperfect. It will remain for future work to indicate the factor, if any, that must be introduced into the subsequent calculations to express this difference appropriately.

Marinelli, Quimby and Hine's paper (1) gives the following formula for expressing the dose from the beta rays of I^{131}:

$D_\beta = 88\ E_\beta\ TC$ equivalent roentgens (e.r.) where
E_β = average energy in MEV of the beta particle = 0.205
T = effective half-life in days of I^{131} in the thyroid
C = concentration of I^{131} in microcuries per gram of tissue.

Thus a concentration of 1 microcurie per gram of thyroid tissue will give the following equivalent roentgens from the beta particles for effective half-lives of I^{131} in the thyroid from 8 to 3 days:

days	8	7	6	5	4	3
e.r.	144	126	108	90	72	54

The method of calculation of the dose from the gamma rays of I^{131} will not be specifically considered here. The maximal gamma ray contribution to the total dose is approximately ten per cent of the contribution from the beta rays, and the combined dose can thus be estimated.

If we assume that a patient with hyperthyroidism receives 5 millicuries of I^{131}, that the gland weighs 30 grams, that the effective half-life of I^{131} in the thyroid is six days and that 70 per cent is retained in the gland, then:

$$D_\beta = 88 \times 0.205 \times 6 \times \frac{5000 \times 0.7}{30}$$

$$= 12{,}800 \text{ e.r.}$$

This dose seems high in comparison with the 2,000 to 3,000 roentgens used in the past for the treatment of hyperthyroidism with external radiation. There are numerous factors which may account for the apparent discrepancy. The number of cases of hyperthyroidism which can be cured with external radiation would appear to be approximately fifty per cent of those treated, whereas the rate of regression from I^{131} following 8,000 or more e.r. per gram of thyroid weight, would appear to be approximately eighty per cent, indicating that the dose delivered by external radiation is possibly less than half the necessary amount. Also, external radiation delivers energy in

a more uniform manner, reaching all the cells of the thyroid. I^{131} delivers its energy to the cells in a central core of a lobe of the thyroid in a fairly uniform manner (variation approximately 40 per cent) but the cells of an outer shell of approximately 2 millimeters thickness receive far less than the maximal dose, leaving a higher percentage of viable cells in this region than would be the case with comparable levels of external radiation.

The relative biologic efficiencies of a roentgen of x-rays and of an equivalent roentgen of beta rays may raise the amount of energy necessary to produce a given biologic effect when delivered by beta particles. Finally the manner in which the energy is delivered to the cells may influence the biologic response. External radiation is commonly given in short, daily exposures of 200 to 300 roentgens until the treatment is completed. The irradiation from I^{131} is spread over several weeks and is continuous. Of the 12,800 equivalent roentgens in the example given above, 8.3 per cent or 1,040 e.r. is delivered in the first day; 8.3 per cent of the remaining 11,760 or 960 e.r., the second day; and so on, reaching 520 e.r. on the sixth day, 260 on the twelfth day and 130 on the eighteenth day. This difference in the manner of administration may well have a major influence on the degree of biologic change per unit of physical energy. Thus our ability to correlate doses under two situations will depend on increasing our knowledge of the manner in which the possible variables may act. The work on human beings will materially assist in the evaluation of the variables if the data are taken and correlated in a valid fashion.

If a patient with cancer of the thyroid is treated with 200 millicuries of I^{131}, the tumor volume is estimated at 200 grams, the effective half-life of I^{131} in the tumor is four days, and 10 per cent of the dose goes to the tumor, then:

$$D_\beta = \frac{72 \times 200{,}000 \times 0.1}{200} = 7{,}200 \text{ e.r./Gm.}$$

With the large doses of I^{131} now used, the radiation received by the total body from radioiodine in the blood becomes a factor in the treatment of patients with cancer of the thyroid, since it would appear that the body may receive from thirty to one hundred equivalent roentgens for each one hundred millicuries administered. Fifty equivalent roentgens would appear to be a fair average. The exact value will be determined by the amount of I^{131} present in the blood. The amount of total body radiation that can be tolerated is not known, but most of the estimates of the acute LD 50 values[1] for man fall between 400 and 600 roentgens. It is reasonable to assume that the radiation to the entire body should be kept as low as possible. In the example given above, fairly typical factors were chosen for

[1] Lethal dose, 50 per cent.

a patient with cancer of the thyroid. They indicate the difficulty in obtaining high radiation levels. Tumors of the thyroid gland are radioresistant and external radiation with doses of approximately 5,000 roentgens does not produce many cures. It is evident, therefore, that great improvement cannot be expected with radioiodine unless some way can be found of increasing the tumor cell's ability to concentrate and retain the isotope.

If a tracer dose of 100 microcuries of I^{131} is to be given to a patient for determination of iodine pick-up, and if we assume a thyroid weight of 25 grams, an effective half-life of 5 days for the iodine, and 50 per cent uptake in the thyroid, then:

$$D_\beta = \frac{88 \times 0.205 \times 5 \times 100 \times 0.5}{25} = 180 \text{ e.r./Gm.}$$

The tolerance or maximum permissible amount of beta or gamma radiation is commonly set at 0.1 r or e.r. per day. When thinking of internally deposited radioactive compounds it is best to take the organ which maximally concentrates or retains the radioactivity as the basis for tolerance calculations. For our purpose it is fortunate that the thyroid concentrates I^{131} so efficiently, since this fact defines the organ which must be protected. In most situations involving other radioisotopes the selection of the limiting organ is a difficult problem, and much experimental and clinical work must be done before other than general, and pessimistic, assumptions can be used in calculations of permissible levels. The fact that I^{131} is not distributed uniformly throughout the gland introduces an element of uncertainty in any calculation of the tolerable amount. It would appear reasonable to assume that the local concentration might increase the amount of energy absorption in local, small areas by a factor of 0.5.

The major uncertainty is in deciding what level of radiation is to be called a maximum permissible or tolerable one. The value of 0.1 roentgen per day recommended by the National Advisory Committee on Radiation Protection for exposure to β or γ radiation is based on the assumption that exposure will be daily over many years, and that no damage will be detectable during the individual's lifetime. While this value clearly should hold for members of the staff working with I^{131} or any other isotope emitting beta or gamma radiations, it would appear to be reasonable to allow, or to accept, a somewhat greater value for the patient on whom investigative or diagnostic studies are to be performed.

If the tolerance value of not more than 0.1 roentgen per day were to hold, the maximal amount of I^{131} which should be used would be 0.0076 microcuries per gram, or 0.19 microcurie for a 25-gram thyroid (1). In a two-week period, the radiation to the thyroid gland would be approxi-

mately 1.0 r. With present day detection equipment it would be impossible to do any investigative work in human beings at this level.

The amount by which the 0.1 roentgen per day figure can be safely exceeded is not known for either external or internally emitted radiations. For chronic exposure in some mammals the evidence indicates that 1.0 r external radiation per day will produce irreversible damage. The relevancy of this information to the situation under discussion is impossible to determine. A more analogous situation may be found in the radiation doses received by the skin during routine diagnostic x-ray examinations. Martin (2) has found that during a gastro-intestinal examination the exposure per film will range from 1 to 8 r, with an average of 5 r. If the assumption is made that 5 films are exposed per examination the average exposure will be 25 roentgens. Insofar as is known, no report exists of chronic damage to the skin following exposure to 25 roentgens. If the time factor is ignored and the transposition from skin to thyroid gland is made, the tentative maximum permissible exposure to the gland would then be 25 roentgens, or 0.19 microcurie of I^{131} per gram of thyroid. It is possible but not easy, using commercially available equipment, to do investigative work with no more than 5 microcuries in the thyroid.

It is appreciated that the bases for selecting the factors leading to the figure of 25 roentgens are at best shaky and at worst irrelevant. The fact that no better assumptions can be made emphasizes the necessity for collecting usable data on animals and humans which ultimately will permit more reliable estimations of the amount of radiation that the thyroid gland may safely assimilate, e.g., the amount which is not carcinogenic.

The approach to the treatment of an otherwise incurable carcinoma of the thyroid is clearly a different problem from that discussed above. Where no other therapeutic agent or approach offers any reasonable hope it is justifiable to use I^{131} in large doses in an attempt to effect a cure or to retard the disease process. The carcinogenic properties are not apt to cause difficulty for some years, if ever, since the life expectancy of the properly selected patient is short. Indeed we should be grateful if the life of an otherwise incurable patient could be prolonged sufficiently to occasion concern about the possibility of tumor induction.

The use of radioiodine in the treatment of nonmalignant diseases of the thyroid should be reserved for those persons in whom the other possible means of therapy have failed, or cannot be used. If all our therapeutic attempts are limited to these classes of patients we can never fairly be charged with irresponsible or heedless use of a potentially dangerous material.

The uncertainties which today attend any estimation of the amount of radioiodine which can safely be administered to a person whose life expec-

tancy is more than a few years warrant discussion of a possible means of reducing the amount of radioiodine necessary to perform any study. The existing gas-filled Geiger-Müller counting tubes have approximately one per cent efficiency, that is, for every 100 gamma rays that pass through the counting tube, one is registered. Deutsch (3) and others observed that it is possible to utilize the fluorescent flash of visible light in certain transparent crystals following the absorption of energy from gamma rays. The development of this technique is receiving much attention in this country today and it may increase the efficiency of our radiation detectors from one per cent to more than fifty per cent. This would mean that the amount of radioiodine needed for a given experiment could be reduced from fifty to one hundred times, which in turn would reduce or eliminate the question of the induction of toxic effects in the patient. It is stressed that these counters are not commercially available today, but we should all be aware of their possibilities and if they do become available should introduce them forthwith into our laboratories.

POTENTIAL HAZARDS

The fact that a hazard to personnel exists has been touched upon during the foregoing section, and the experimental and clinical evidence for the necessity of protective measures is summarized here. The physiologic dysfunctions occasioned by exposure to radiations have been known for sometime either by observation in people unfortunate enough to have had overexposure to either external radiations or to internally deposited radioisotopes, or through experiments in animals designed to test and to give more or less quantitative information about these dysfunctions. As a result, we know that four classes or types of damage may result. These are; the induction of neoplasms, the production of blood dyscrasias, the production of genetic change, and shortening of the span of life.

The induction of neoplasms is now established in both man and animals as a late effect of overexposure to radiations. The story of the radium-dial painters and radium-water drinkers is too well known to detail here, except to say that approximately 20 osteogenic sarcomas have been reported in these groups. The amounts of radiation necessary to produce these tumors is not yet fixed certainly but would appear to be approximately 1 to 2 equivalent roentgens per day per gram of bone, or approximately one microgram of radium fixed in the skeleton. In animals it has been possible to produce tumors of the skin, connective tissue, bone, intestinal tract, and lymph nodes. Preliminary data indicate, that as the concentration is reduced by a factor of ten, the time necessary to induce a tumor is doubled. For example, if one microcurie per gram of body weight is capable of inducing a tumor in 200 days, 0.1 microcurie per gram body weight may be

expected to induce the tumor in 400 days. It is of considerable importance to know more definitely the effect of concentration and time of action with regard to the incidence of tumor production. We also need to know the length of time the insult needs to act before an irreversible process leading to cancer has been initiated. It often has been said that no hazard is present because the half-life of a given radioisotope is so short. Preliminary results at the Argonne National Laboratory indicate that the time of appearance of leukemias in susceptible mice is shortened after single injections of P^{32}. While it cannot be assumed that the mechanisms involved in this effect are the same as those involved in the *de novo* production of a tumor, the observation does point to the necessity for obtaining data on the time through which radiations must act before irreversible changes leading to neoplasms occur. Until such data have been obtained we should all be aware of our uncertainty on this point.

Protection of potentially exposed persons depends on the education of the worker, on the provision of adequate equipment with which to work, on the establishment of means to follow the state of health of the worker, and the establishment of a system for routinely determining the level of radiation on material objects in his work area. Education of all persons in the techniques they need to protect themselves from overexposure to external radiation and radioactive materials is essential to any program for protection. It must extend to all levels, from the physician who is to assist in the overall planning to the orderly who is to collect the urines. Each person must have the knowledge necessary to the satisfactory, safe performance of his job. If this knowledge is lacking, the best equipment in the world will not prevent injuries resulting from overexposure to radioactive materials.

Since the kinds of hazards vary with the radioisotopes to be handled, and with the job to be done, the equipment needed for protection will also vary. Protection against external (beta, gamma) radiations depends primarily upon the interposition of enough absorbing material between the source of radiation and the worker to reduce the intensity of radiation satisfactorily. This objective is easy to achieve in many circumstances such as during the storage and transportation of radioiodine, but when chemical procedures must be carried out the problem becomes more difficult. Depending on the amount and kind of activity involved, more or less complicated apparatus is needed to prevent overexposure of the hands or other parts of the body. Devices for manipulating radioactive material safely are described by Tompkins, Broido and Teresi (4). It is fortunate that much or even most of the work done with tracer quantities of radioiodine will not require elaborate equipment for protection against external radiation.

Protection against the deposition of radioiodine internally is more diffi-

cult and perhaps more important than protection against sources of external radiation. For this kind of protection it is necessary to arrange that radioactive materials cannot enter the body through the lungs, the intestinal tract, or the skin. Of the potential routes, inhalation would appear to be the most hazardous in situations where solutions are used. Experience has shown that the provision of adequate ventilation, the arrangement of working conditions so that the air breathed by the worker is not first contaminated with radioiodine, will minimize or eliminate the possibility of radioactive material entering the body through the lungs. This means that all work involving chemical manipulation of solutions containing more than a few microcuries of radioiodine should be done in a hood with a good draft.

Ingestion is primarily a problem of skin contamination with consequent secondary transfer to the mouth. If rubber gloves are worn during the periods of potential contamination and if the hands are washed after the gloves are removed the likelihood of ingesting radioiodine is reduced. If large amounts of radioiodine are to be processed, consideration should be given to the provision of special clothing and shoes to be worn only when working with the highly active preparations. Particular attention should be given to the prevention of contamination of breaks in the skin since such information as is available indicates that dangerous and possibly lethal amounts of some radioactive materials can be introduced into the body in this way.

Some means for regularly determining the state of health of exposed individuals is necessary both from the medical and legal viewpoints. A program for the evaluation of the worker's health should include periodic physical examinations and blood counts. The usual tests of thyroid function should be made on persons immediately concerned with the preparation of the radioactive compounds or solutions. Consideration should be given to determining the amount of I^{131} in the thyroid or in the urine at regular intervals as a check in the individual on the adequacy of the measures taken to protect him. Certainly these determinations should be done after known or suspected contamination with radioiodine has occurred.

A monitoring program for the routine estimation of the amount of radiation received by all potentially exposed personnel should be included in any program for the protection of the worker's health. Film badges or pocket ionization meters will give adequate estimations of the amount of exposure to gamma and hard beta rays. Unfortunately no satisfactory device for determining the degree of exposure to beta particles of the usually encountered energies is available.

When using radioiodine clinically the operations which appear to present the greatest potential hazards are the opening of the shipping container, preparation of the stock solution, delivery of the solution to the patient,

administration of the radioiodine, collection and storage of excreta for biochemical data, and disposal of the unwanted radioiodine. When therapeutic doses are given the recipient should be isolated so that no question of irradiation of other patients can arise. Highly active solutions of radioiodine should be stored to permit decay of the radioactivity prior to disposal of the liquid.

Two other aspects of the problem of control of radiations deserve mention. They are the possibility of legal action and the danger of contamination of equipment or other material objects. The protection of property usually necessitates the performance of routine surveys for the degree of radioactivity in all areas in which radioiodine is handled. The legal hazards concern the possibility of suit by the patient or his family, by employees of the hospital, and by members of the community. The possibility of action by the patient or his family is an old familiar problem and has been met for years by departments of radiotherapy and need not detain us here. Protection against suit by employees will usually require that records of their exposure and of the results of physical and laboratory examinations made on them be kept in a legally satisfactory manner. The possibility of suit by a member of the community may be met by the installation of equipment and techniques to prevent the exposure of the community to discarded radioactive materials.

SUMMARY

The desirability of knowing as accurately as possible the amount of radiation received by the thyroid has been discussed together with the uncertainties associated with the calculations employed. The imperative need for determining as soon as possible the amounts of I^{131} which are carcinogenic or otherwise toxic to the normal organism and the importance of the current and future clinical work in the resolution of the present uncertainty is stressed. The need for constant awareness of the toxic properties of radioactive materials when conducting investigative or diagnostic studies in human beings is of great importance. Recognition of these properties necessitates the use of the least possible amount of radioiodine for such studies.

The need for protection of the worker against radiations and radioactive materials is based on the known toxic or lethal effect of prolonged exposure to these agents. When establishing measures for protection, the needs of the worker, his associates, the community, and of property must be considered. Specialized equipment must frequently be provided to insure that proper working conditions are available. The efficiency of the program must be checked by periodic determinations of the health of the individual and by a biophysical monitoring program. Education of all persons who are to

handle radioiodine in the proper safe methods for performing their jobs is a sine qua non.

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A STUDY OF THE HISTOPATHOLOGY AND PHYSIOLOGIC FUNCTION OF THYROID TUMORS, USING RADIOACTIVE IODINE AND RADIOAUTOGRAPHY*†

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AT THE meeting of this Society one year ago we presented some observations (1) on the capacity of various types of thyroid tumors to collect radioiodine and briefly reviewed the pertinent literature dealing with the iodine and radioiodine content of such tissues. Our former observations were made by digesting known weights of thyroid tissue and counting the radioactivity in the iodine which was precipitated from the liquid digest.

We found that undifferentiated tumors in general showed relatively less avidity for radioiodine than some more differentiated ones. We also found, in that group, a few benign tumors which contained more of an administered dose of radioiodine per unit weight than the remaining thyroid tissue. Shortly before our report was given, Leblond *et al.* (2) and Puppel, Leblond and Curtis (3) reported that all nodules in 7 cases of nodular goiter contained less radioiodine and were therefore functionally less active than the remaining thyroid tissue.

In years gone by, Wegelin (4) showed that adenomatous tissue from the thyroid when fed to tadpoles caused less growth than the extra-adenomatous tissue. Branovacky (5), on the other hand, using a similar assay method, found some toxic nodular goiters that were more active than diffuse hyperplastic goiters, but it is not clear whether the tissue samples came from the nodules or from the intervening tissue.

The existence of true hyperfunctioning adenomas has been questioned by many; however, others have expressed the belief that they do exist and have supported this idea by calling attention to physiologic atrophy of the remaining thyroid tissue (Wilson (6), Rice (7), Hendrick (8), Cope *et al.* (9) and Plummer (10)).

In this study radioautographs have been used to acquire further knowledge of the function of thyroid tumors. This technic has made possible a correlation between the histologic features of the tissues and the localiza-

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tion of the activity. The occasional spotty distribution of radioiodine in tumors, as found in some autoradiographs has shown that sampling masses of tissue by chemical means may give misleading results.

For the purpose of this study the term "adenoma" has been used to describe any completely encapsulated discrete tissue mass in which the histologic pattern is different from the remaining thyroid tissue. In a physiologic study such as this, one basic assumption is made which is already rather universally accepted. The assumption is that the degree of affinity for radioiodine represents the degree of function of the thyroid tissue. Thus if two samples of tissue in the same subject are exposed to the same opportunity to collect iodine and one collects more iodine per unit weight than the other, its function is greater. The term "hyperfunctioning" is therefore used to describe an adenoma which by its increased affinity for a tracer dose of iodine is functioning or utilizing iodine in excess of the remaining thyroid tissue.

There are three features of this study which we should like to present:

1. The degree of function may be related to the degree of cellular differentiation of adenomas, with certain exceptions.

2. There are hyperplastic adenomas with cellular hypertrophy which are hyperfunctioning but there are also hyperplastic adenomas which are not functioning.

3. Hyperfunctioning adenomas may exist with or without evidence of thyrotoxicosis and probably by their excessive activity suppress otherwise normal thyroid tissue.

A radioautographic technic has been used to study the affinity for iodine or function of thyroid adenomas in 94 cases of nodular goiter.

All patients were given an identical standard tracer dose of radioactive iodine (I^{131}) twenty-four to seventy-two hours before surgery. The nodules were removed together with an adjacent piece of thyroid tissue. The block composed of both types of tissue was prepared by a rapid histologic technic, mounted on slides and exposed to film. Six radioautographs, each with a different exposure time, were made of each adenoma.

The terminology and classifications of adenomas are so confusing that we prefer to deal in pictures rather than names. If the adenomas are arranged as a spectrum beginning with the least differentiated or most embryonal and progressing onward to the most differentiated types, just as we observed in embryonic development, we find that in general the degree of differentiation runs parallel to the degree of function.

In Figure 1 we have some representative samples of such a spectrum; a) a solid cellular fetal adenoma or embryonal adenoma; b) an adenoma with solid strands of cells and very primitive acini (trabecularis and tubularis, Wegelin); c) an adenoma with minute acini (microfollicularis, Wegelin);

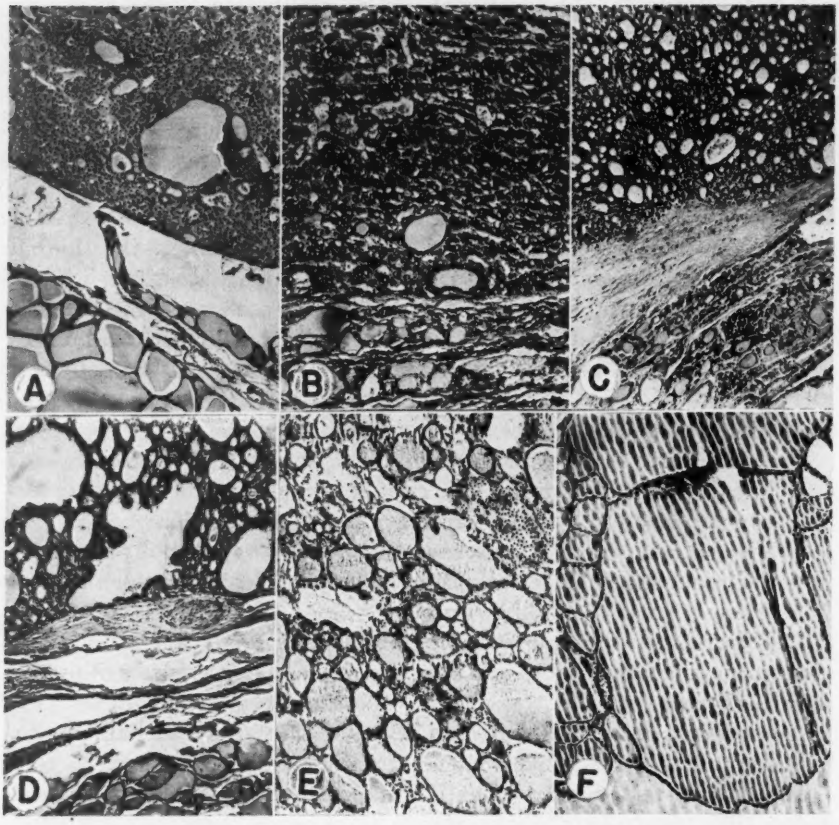

FIG. 1. Some representative samples of a spectrum of adenomas arranged according to the degree of differentiation.

A. Solid cellular or embryonal adenoma; slight evidence of acinus formation (same tissue as represented in Fig. 2).
B. Solid strands of cells with very rare suggestion of early acini (same tissue as adenoma on the right in Fig. 3) (struma nodosum trabecularis et tubularis, Wegelin).
C. Minute acini (struma nodosum microfollicularis, Wegelin).
D. Hyperplastic, with large and small acini (same tissue as in Fig. 4).
E. Mixed large and small acini with colloid (struma nodosum micro et macrofollicularis, Wegelin).
F. Predominantly large acini distended with deep-staining colloid (macrofollicularis, Wegelin).

d) a hyperplastic adenoma with large and small acini; e) mixed large and small acini with colloid (micro et macrofollicularis, Wegelin); f) an adenoma with large acini (macrofollicularis, Wegelin), colloid adenoma.

The next illustrations represent similar histologic patterns with the radioautographic image produced by each tissue. The darkened areas represent the location of the radioiodine. Figure 2 represents an undifferentiated solid cellular embryonal adenoma without function, as evidenced by the lack of radioiodine in the adenoma. Figure 3 represents two adenomas in the same lobe: one similar to the preceding one without function; a second with very primitive acini with slight function compared to the remaining thyroid tissue. In the more differentiated end of the spectrum we find a hyperplastic adenoma (Fig. 4) with cellular hypertrophy and with excess function. There are also at the more differentiated end of the spectrum two exceptions to the parallelism of function and differentiation. One of these is the (Fig. 5) colloid adenoma which has diminishing function and is in-

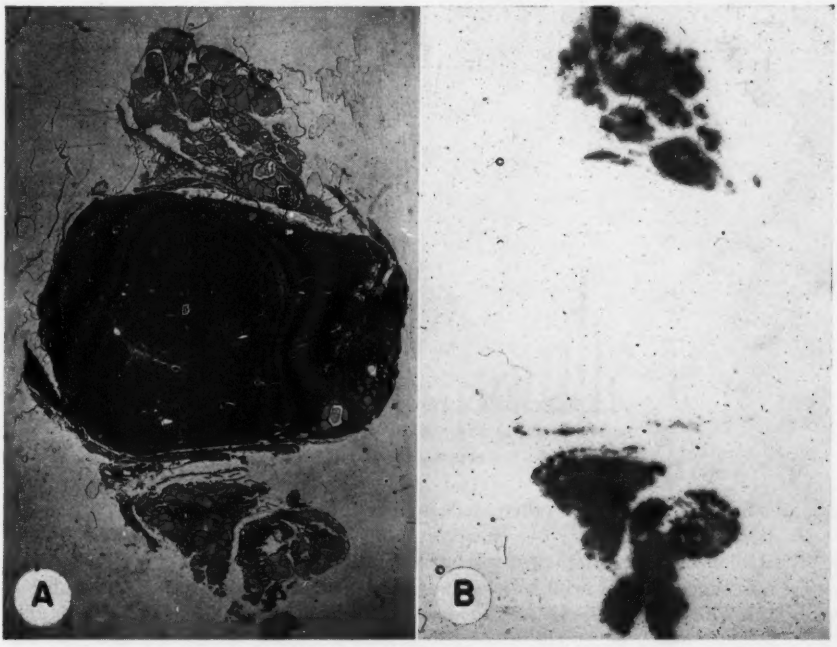

FIG. 2. A solid cellular or embryonal adenoma without acini.

A. Histologic section.

B. Radioautograph showing no evidence of function in the adenoma. The areas of blackening coincide with the normal thyroid tissue.

terpreted as being in a resting or "overripe" stage. The other exception is a group of hyperplastic adenomas with cellular hypertrophy without function, of which we shall speak later.

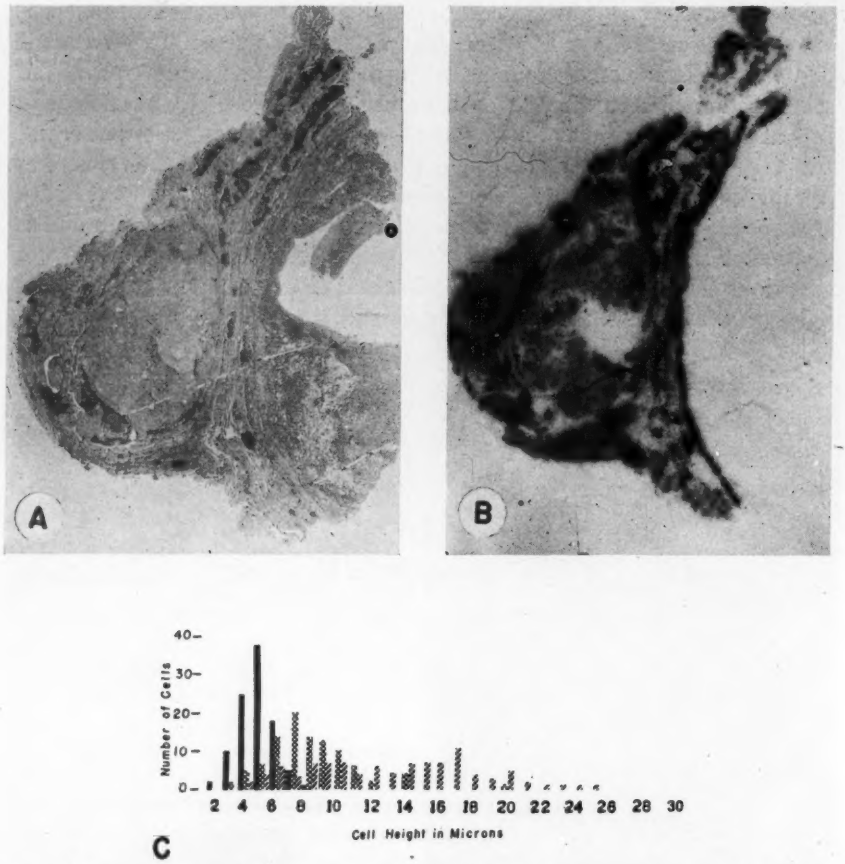

FIG. 3. Two adenomas with different degrees of differentiation, in the same patient.

A. Histologic section.

B. Radioautograph. On the right, an adenoma composed of solid strands of cells and rare suggestions of acini without function; there is some necrosis in the center of this adenoma: on the left, an adenoma composed of many tiny acini; slight function as compared to the surrounding normal thyroid itssue, which shows the greatest degree of blackening.

C. Cell heights (100 cells of each type of tissue). Black columns represent extranodular tissue; diagonal hatched columns represent the cells of the adenoma on the right; checkered columns represent the cells of the adenoma on the left. Note the latter has somewhat more uniformity of cell height, consistent with more function.

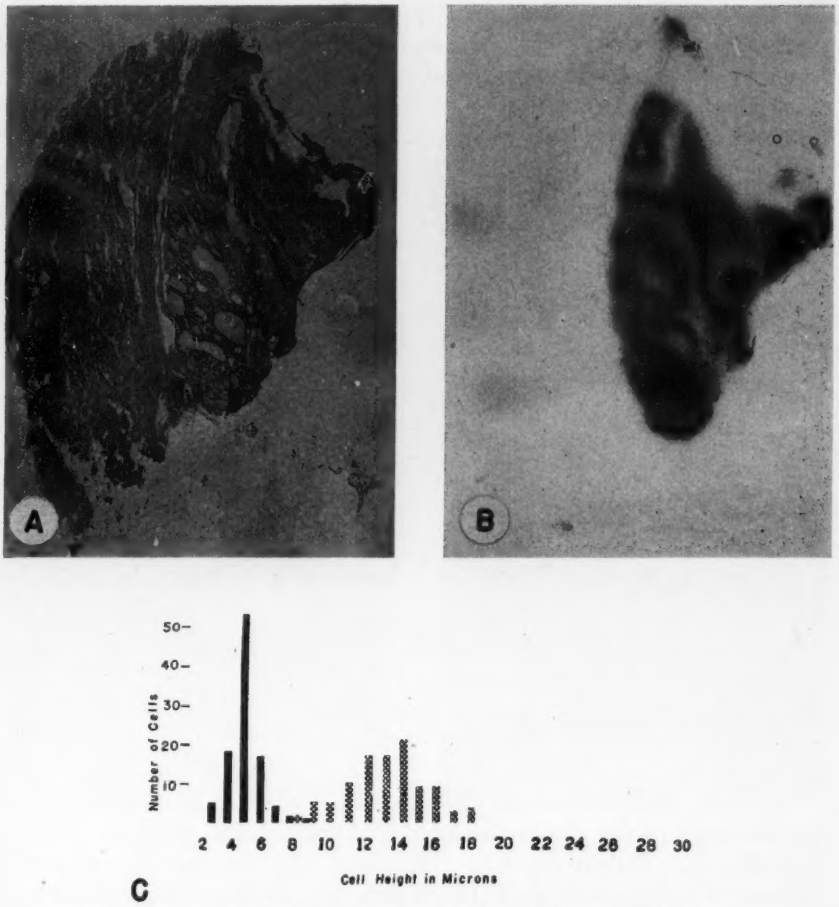

FIG. 4. Hyperplastic adenoma with cellular hypertrophy.

A. Histologic section. A roughly triangular piece of adenoma on the right; uninvolved thyroid tissue on the left.

B. Radioautograph showing the relatively high concentration of radioiodine in the adenoma and practically none in the remaining thyroid tissue. This adenoma is thus interpreted as being a hyperfunctioning adenoma because it is functioning in excess of the remaining thyroid tissue.

C. Cell heights (100 cells in each type of tissue). Black columns represent cells in the uninvolved thyroid tissue; checkered columns represent the cells of the adenoma. This illustrates the relatively uniform cellular hypertrophy of hyperfunctioning adenomas.

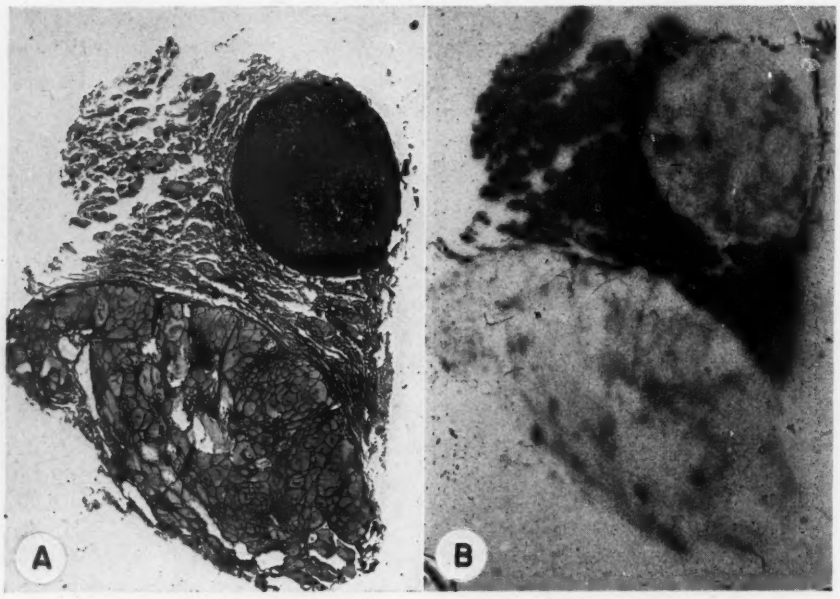

FIG. 5. A colloid adenoma (below) with relatively little function.

A. Histologic section. A colloid adenoma (below) and a solid cellular adenoma with a few small scattered acini (upper right)

B. Radioautograph. The colloid adenoma with large distended acini and flat epithelium is looked upon as being in a resting or "overripe" stage of development.

For years efforts have been made to relate hypertrophy and hyperplasia in adenomas to the clinical features of thyrotoxicosis (Goetsch (11, 12), Boothby (13), Wilson (6), Key (14), Gray (15), Parsons (16), Rice (17), Rabinovitch (18), Delli Bovi (19), Welch (20), Broders (21), Wyrens (22), Johnson (23) and Martin (24). In nodular goiter with thyrotoxicosis a hyperplastic adenoma is often but not always identified. On the other hand there is frequently found an adenoma which by all known histologic criteria appears to be hyperfunctioning but the patient has no evidence of thyrotoxicosis. This has been a perplexing problem which so far has not been solved by purely histologic means. The question then arises as to which hyperplastic adenomas are functioning and which are not. And further, are hyperfunctioning adenomas present in patients who do not have thyrotoxicosis?

Although all the histologic features of the nucleus, cytoplasm, and colloid from these adenomas were tabulated, in this discussion only a few comments on the cell height are to be made. A representative cell of each

of 50 to 100 acini was measured with a micrometer when the cells were observed under oil immersion. Many hyperplastic adenomas with cellular hypertrophy were found. Some of these adenomas contained excessive amounts of radioiodine, others had practically none, yet there was a striking increase in mean cell height of both types. Figure 6 is an example of an adenoma with a considerable increase in the average cell height, yet there

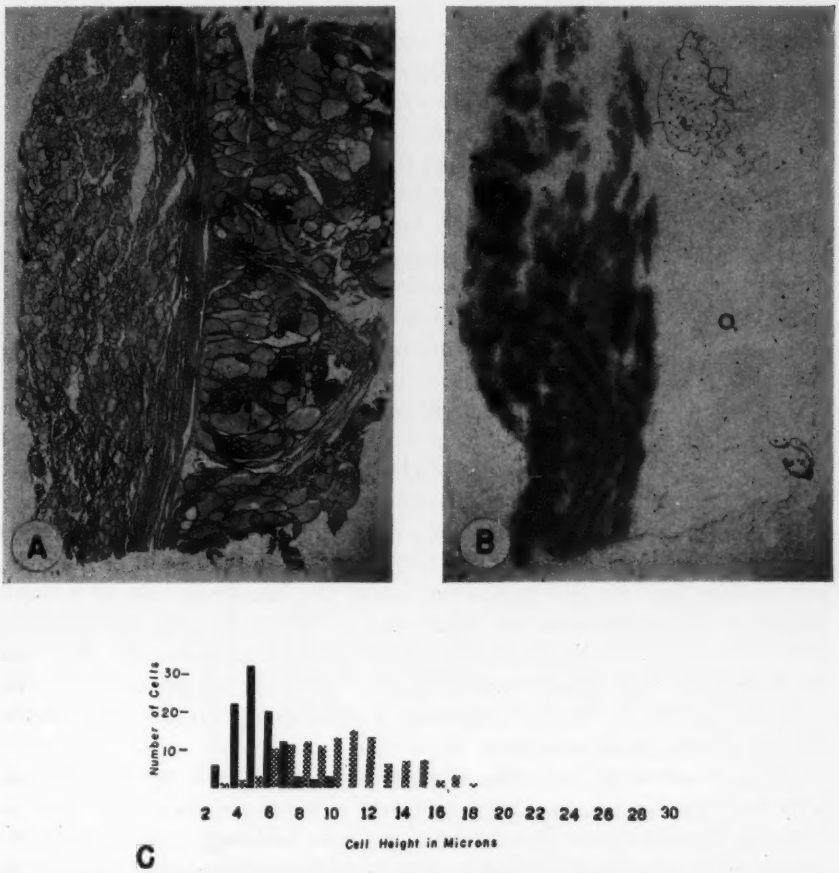

FIG. 6. A hyperplastic adenoma without function.

A. Histologic section. Adenoma on right; extranodular tissue on left.

B. Radioautograph, showing the radioiodine in the extranodular tissue rather than in the adenoma.

C. Cell heights (100 cells in each type of tissue). Black columns represent the cells in extranodular tissue; checkered columns represent the cells of the adenoma, and show an increased mean cell height but with considerable variability.

is no function as seen from the radioautograph made from that tissue. Figure 7 is another example of an adenoma with an increase in the average cell height but here the function is excessive as demonstrated by the striking concentration of radioiodine in the adenoma. If the range of variability in the height of the cells was considered rather than just the average, it was found that those adenomas such as this one with excessive function (Fig. 7) had a rather uniform increase in cell height, whereas nonfunctioning adenomas, such as that in Figure 6, are composed of cells whose height covered a noticeably wider range. This relation of the uniformity of cell height to increased function on one hand and the variability of cell height to diminished or absent function on the other hand held true in most of the benign tumors that were studied.

Among all of the patients studied there were 16 who had carcinoma, a diagnosis that was confirmed by several pathologists. Nine of these were papillary adenocarcinomas, and 4 were alveolar adenocarcinomas. The remainder were highly undifferentiated carcinomas. The impression was gained from studying the hyperplastic adenomas which had no function, that these tumors as a group had more and more irregularity in cell height and more and more papillary formation until the frank papillary adenocarcinomas were reached. Figure 8 illustrates samples of such a spectrum. At the top of this figure there is an hyperfunctioning hyperplastic adenoma with a uniform increase in cell height. The next adenoma (in same figure) is one with negligible function and slightly greater variability in cell height. The next adenoma is very hyperplastic and considered by some a papillary cystadenoma and by others a borderline papillary malignancy. In this adenoma there is considerably greater variability in the height of the cells, and no function. Finally at the bottom of the figure the cells of a frank papillary adenocarcinoma are represented. This tumor has no function. The variation in the height of the cells is extreme. It is possible that this large group of hyperplastic nonfunctioning growths, as represented by the lower 3 examples in Figure 8 represent a spectrum of tumors which shade into papillary adenocarcinoma.

Let us turn to the hyperfunctioning adenomas. These are classified as hyperfunctioning because they collected more radioiodine than the remaining thyroid tissue. Twenty-eight patients had such tumors. In 14 instances they were single; in 9 they were multiple and similar; in 7 there was at least one adenoma functioning in excess among others which were not functioning. If we consider those cases which had only nodules that were functioning in excess of the remaining thyroid tissue we find that the basal metabolic rate ranged from plus 35 down to minus 19. Except in some of the cases where the basal metabolic rate was initially low, there was a prompt decline in the rate after the nodules were removed. In cases where

observations could be continued there was apparent subsequent compensation and the basal metabolic rate later returned to a more normal range.

In many cases where there was definite evidence of toxicity the mean cell

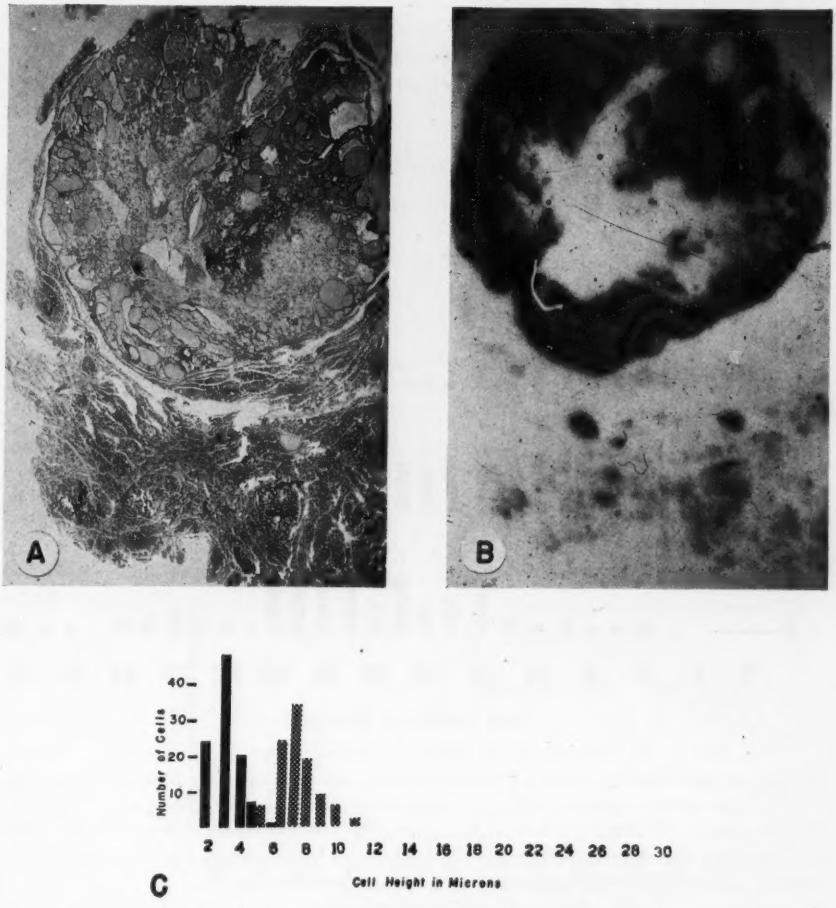

FIG. 7. A hyperfunctioning adenoma.

A. Histologic section.

B. Radioautograph. The blackening shows a higher concentration of radioiodine and thus greater function in the adenoma. Note the necrosis and lack of function in the center of the adenoma.

C. Cell heights (100 cells in each type of tissue). The height of the cells of the extranodular or remaining thyroid tissue (black columns) is depressed below the normal average. The cells heights (checkered columns) in the adenoma are increased. There is rather uniform cellular hypertrophy in the adenoma. Several other hyperfunctioning adenomas were found in this same thyroid.

height of the remaining thyroid tissue was depressed below the usual normal range as seen in the case represented at the top of Figure 9; but in cases where the basal metabolic rate was not elevated and toxicity was absent,

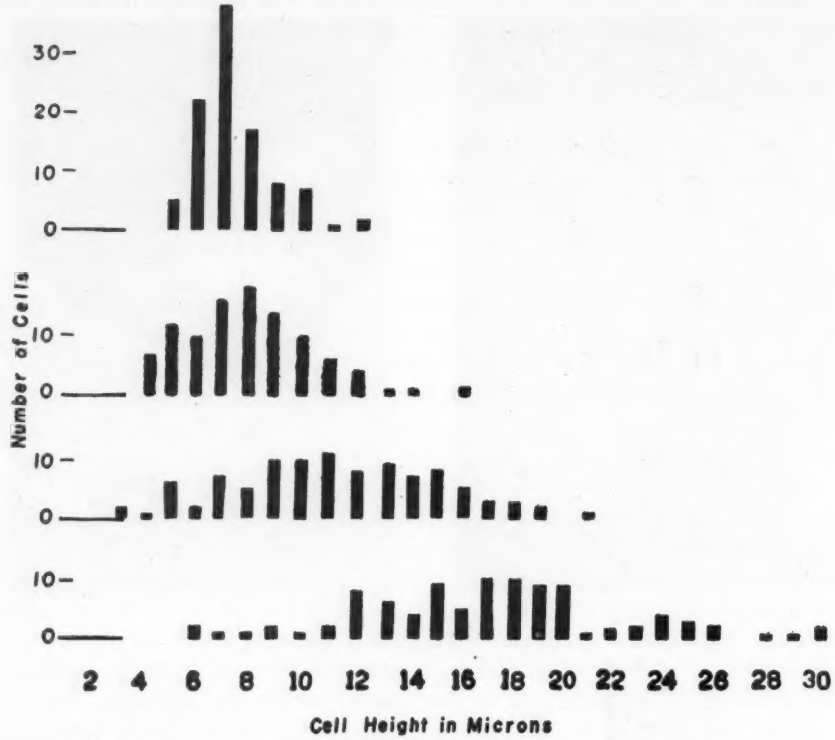

FIG. 8. The pattern of cell height in several hyperplastic tumors.
The tumors from the top down are: a hyperplastic hyperfunctioning adenoma composed of cells with rather uniform height; a hyperplastic slightly functioning adenoma with slightly greater variability in cell height; a papillary cystadenoma without function and still greater variability in cell height; a papillary adenocarcinoma with metastases—extreme variability in cell height and no function (see also Fig. 6).

the cell height of the paranodular tissue was not depressed, as in the case represented at the bottom of the same figure.

In numerous cases there was apparently sufficient necrosis or the tumor had not reached sufficient size to cause clinical symptoms.

A very instructive case should be mentioned at this time. This was a woman aged 31 who was first seen six months before thyroidectomy. There was a six-year history of a single nodule in the thyroid with reported mild elevations in basal metabolic rate for five years. When first seen by us six

months before thyroidectomy, she had frank thyrotoxicosis. Although thyroidectomy was recommended, unavoidable circumstances made it impossible for the patient to enter the hospital at that time. She returned six months later for thyroidectomy, at which time the nodule had not changed by physical examination, but the thyrotoxicosis had practically vanished. As seen in Figure 10, the nodule was a hyperfunctioning adenoma. The entire center of the nodule was found to be necrotic, although a rind of

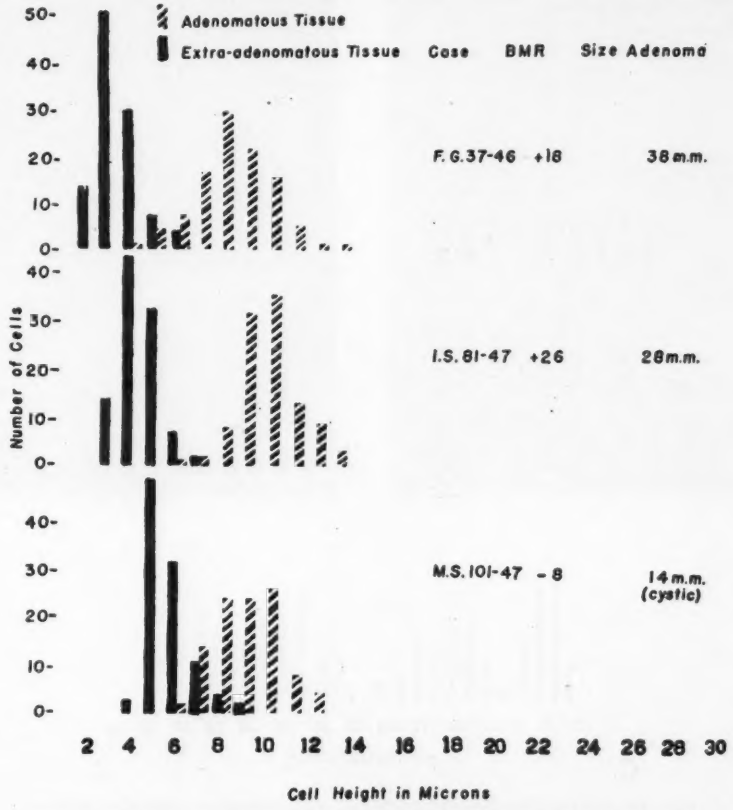

FIG. 9. Depression of the cell height of the remaining thyroid tissue in cases with hyperfunctioning adenoma and thyrotoxicosis.

Cell heights of adenomas represented by shaded columns; cell heights of remaining thyroid tissue with diminished or absent function represented by black columns. At the bottom—a case without thyrotoxicosis with a small single hyperfunctioning adenoma whose total function is apparently insufficient to suppress the normal thyroid tissue. At the top—a case with thyrotoxicosis with a single but large hyperfunctioning adenoma whose total function apparently oversupplies the biologic demand for thyroid hormone, resulting in atrophy of the cells of the remaining thyroid.

hyperfunctioning tissue remained just under the capsule. One is tempted to speculate that this necrosis took place in the intervening six months and accounted for the disappearance of the symptoms.

Old and recent necrosis was a very common finding in the hyperfunction-

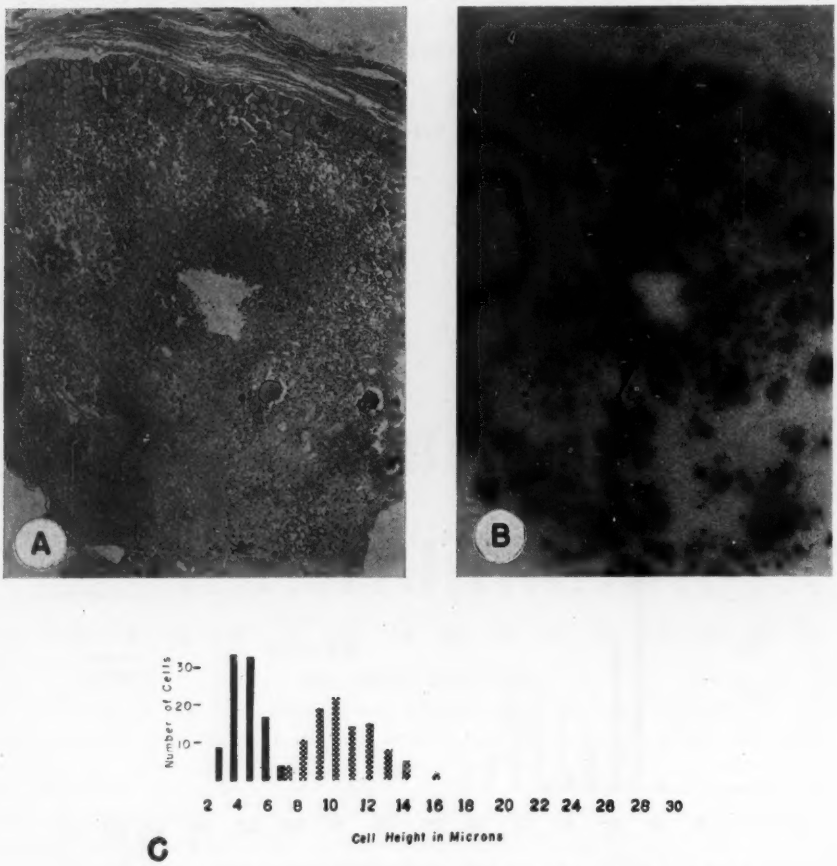

FIG. 10. A hyperfunctioning adenoma with extensive necrosis, from a patient who had had thyrotoxicosis several months before.

Diameter of adenoma 36 mm.

A. Histologic section. Adenoma with necrosis (remaining or extra-nodular atrophic tissue above).

B. Radioautograph. Note lack of function, indicated by the lack of blackening, in degenerated areas of the adenoma and in the extra-nodular tissue.

C. Cell heights (100 cells of each type of tissue). Black columns represent the cells of the extranodular or remaining thyroid tissue; checkered columns represent the cells of the adenoma.

ing adenomas even though the adenomas may have been small. On the other hand, hyperplastic adenomas without function were found to have necrosis rather infrequently, especially when these adenomas were small.

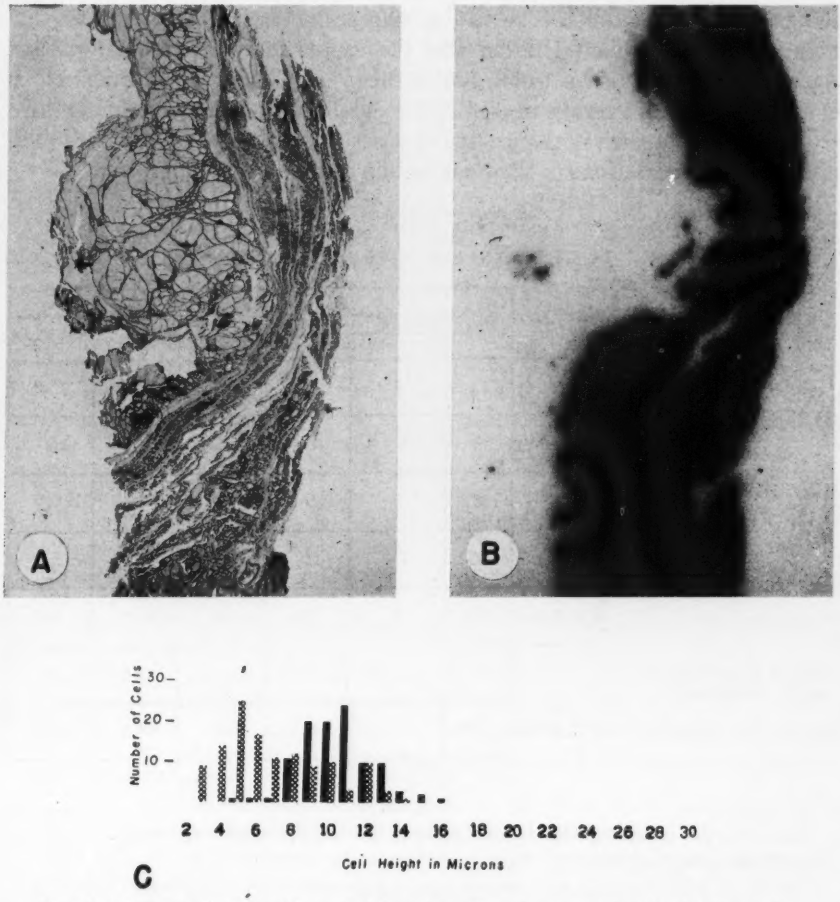

FIG. 11. Graves' disease with an incidental nonfunctioning nodule in the thyroid.

A. Histologic section.

B. Radioautograph showing striking concentration of the radioiodine in the thyroid tissue other than the nodule, thus indicating that the extranodular tissue was responsible for the excessive function.

C. Cell heights (100 cells of each type of tissue). Checkered columns represent cells of the adenoma, a cell height pattern commonly found in a colloid adenoma. The black columns represent the cells of the extranodular tissue. These cells of the extranodular tissue average 11 microns in height as compared to 5 microns usually found in normal thyroids.

One final observation should be mentioned. A mildly toxic patient with the eye signs commonly associated with Graves' disease had a single nodule in the thyroid on physical examination. There was considerable difference of opinion as to whether this nodule might be responsible for the patient's symptoms. The radioautograph (Fig. 11) shows how the nodule was an incidental lesion and the excess function came from the remaining thyroid tissue which had a mean cell height of 11 microns as compared with an average of 5 microns usually found in normal thyroids.

Figure 12 summarizes the groups of cases that have been described and illustrates the variations in basal metabolic rate that were found.

THE RELATION OF THE FUNCTION OF ADENOMAS TO THE BASAL METABOLIC RATE

		TOTAL CASES	BASAL METABOLIC RATE				
			NUMBER OF CASES		LOWEST	HIGHEST	AVERAGE
			+10 or above	below +10			
HYPERFUNCTIONING	SINGLE	13	4	9	-19	+27	+1.6
	MULTIPLE	9	6	3	-12	+35	+11.1
MULTIPLE HYPO and HYPER FUNCTIONING		6	1	5	-8	+37	+6.6
HYPOFUNCTIONING	SINGLE	15	0	15	-16	+9	-3.6
	MULTIPLE	20	2	18	-19	+11	-4.0
GRAVE'S DISEASE with ADENOMA		1	1	-	-	+26	-
MULTIPLE NON-ENCAPSULATED		7	1	6	-8	+46	+6.5

* frank thyrotoxicosis

FIG. 12.

All 94 cases of nodular goiter do not appear in the table because some were examples of thyroiditis, cancer, cysts, etc.

SUMMARY

Radioautographs have been prepared from thyroid tumors removed from patients who had previously received tracer doses of radioactive iodine. The ability of thyroid tissues to collect and fix radioiodine has been used to interpret the function of such tissue.

There is a parallelism between the degree of function and the degree of cellular differentiation of adenomas, with certain exceptions.

There are adenomas which have cellular hypertrophy and hyperplasia and which hyperfunction, but there are also adenomas which have cellular

hypertrophy and hyperplasia and which scarcely function at all. The latter group with negligible function shows increased variability in the cell height and in this respect appears to shade off into the class of tumors known as papillary adenocarcinoma.

Adenomas which are functioning in excess of the remaining thyroid tissue may occur with or without an elevation in the basal metabolic rate. By their action they apparently suppress the function of the remaining thyroid tissue, depending on the magnitude of their contribution to the total biologic demand for thyroid hormone.

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CANCER OF THE THYROID IN A THYROID CLINIC*

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CANCER of the thyroid gland has aroused considerable interest for many years. It still, however, remains a subject for discussion and controversy, not only in regard to etiology, but also prognosis and criteria for diagnosis and treatment. The pathology seen in the malignant thyroid tumors of patients treated at the Lahey Clinic has been recently reviewed, and certain aspects are herewith presented in the hope that this study, coupled with others of a similar nature, may assist eventually in clarifying some of these controversial issues.

The purpose of this presentation is fourfold: first, to bring up to date the number and pathologic types of thyroid cancers seen at this clinic; second, to set forth the criteria used pathologically for the diagnosis of thyroid cancer and for the classification of the tumors into the various groups; third, to consider the clinical usefulness of pathologic diagnoses based on these criteria; and fourth, to set down the surgical approach to such groups.

The material reviewed consists of the pathology of the thyroid cancer specimens removed by surgeons at the Lahey Clinic during the past twenty years (1928 to 1947 inclusive). In this period, over 19,000 thyroid operations were performed. The 439 specimens of cancer, representing an incidence of 2.3 per cent, came from operations ranging from biopsies to total thyroidectomies and radical neck dissections. The histologic appearance of each of the 439 cancer specimens has been reviewed to insure uniformity of application of classifying criteria.

The incidence of the various types of cancer is presented in Table 1. The classification used is similar to that reported by Lahey, Hare, and Warren (1, 2), with slight modifications to result in simplification.

CRITERIA FOR DIAGNOSIS OF CANCER

The pathologist must make the diagnosis of thyroid cancer largely on microscopic evidence; the clinical history and gross appearance are too often equivocal, and the specimen submitted may be only a biopsy of the lesion. The histologic criteria used to diagnose well-developed or more highly malignant cancers of the thyroid are essentially the same as the

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criteria used for diagnosing cancer in other structures in the body. Among the more important are such things, for example, as evidence of active cellular growth (numerous mitoses), an atypical growth pattern, atypical cells, and invasion of adjacent normal structures such as stroma, blood vessels or lymphatics. The majority of thyroid cancers (Group II and Group III, Table 1) show many such definite criteria and therefore give the pathologist little difficulty in making a diagnosis of malignant disease.

Obviously, however, some cancers of the thyroid at the time they are seen pathologically, will be early and as a result, poorly developed; simi-

TABLE 1. CLASSIFICATION OF THYROID CANCER

		Number	*Per cent*
Group I: Adenoma with invasion		108	24.6
a. Blood vessel invasion	12		
b. Capsular or lymphatic invasion	61		
c. Capsular or lymphatic plus blood vessel invasion	35		
Group II: Adenocarcinoma		203	46.2
a. Papillary type	154		
b. Alveolar type	49		
Group III: Carcinoma Simplex		108	24.6
a. Small cell type	72		
b. Giant cell type	36		
Miscellaneous		20	4.6
a. Hürthle cell	7		
b. Fibrosarcoma	7		
c. Lymphoma	3		
d. Epidermoid	2		
e. Unclassified	1		
TOTAL		439	100

larly, others will be of very low grade malignancy. These early or low grade cancers are considerably more difficult to diagnose, since many or most of the usual histologic criteria for a malignant tumor may be lacking.

It is important, nevertheless, to recognize cancer of this character, since with adequate treatment the rate of cure should be very high. It is customary to assume that most thyroid cancers arise from pre-existing benign

adenomas; it is the adenomas, then, that should be examined carefully for evidence of early malignant change. The criterion which appears to be the most useful for the diagnosis of early or low grade cancer arising in an adenoma, is invasion of blood vessels, lymphatics or the capsule. Adenomas which show such invasion but are otherwise microscopically benign are considered to be the earliest stage of cancer which can be diagnosed histologically.

CRITERIA FOR CLASSIFICATION OF CANCER

Practically all the malignant thyroid tumors are epithelial and can be classified into three groups (Table 1). There are only a few miscellaneous, rare or unclassified cancers which cannot be included under one of the three headings.

Group 1 of thyroid cancers makes up 24.6 per cent of the total. It consists of those thyroid tumors which show invasion of blood vessels, lymphatics or capsule as the only evidence of malignancy. Benign epithelial thyroid neoplasms may be nonpapillary (the fetal adenoma being a typical example) or papillary (papillary adenocystoma) and the invasion as described may be found in either type. Tumors included in Group I cannot be diagnosed as cancer except by microscopic examination. Since they are early or low grade, the expected cure rate should be high and metastases infrequent. If, however, metastases occur (and it is not possible to estimate histologically in which cases they will or will not occur), the type of invasion should give an indication as to their probable site: with blood vessel invasion, distant metastases may occur, whereas if the invasion is of lymphatics or capsule, the extension might be expected in the regional lymph nodes or the adjacent thyroid parenchyma. At times, of course, all types of invasion may be found in the same tumor (Figs. 1 and 2).

It is probable that there are other equally early cancers which do not arise from adenomas. These should also be included in Group 1, but unfortunately, the criteria for the segregation of such neoplasms are not sufficiently defined as yet.

Tumors in Group II are called adenocarcinomas and represent 46.2 per cent of the total cancers. They have a clinical history and a gross appearance which are much more suggestive of cancer than Group I. Histologically they may be divided into papillary and nonpapillary (alveolar) types and they often give the impression of being merely a more advanced stage of the Group I lesions. In addition to invasion, numerous other unequivocal signs of malignancy are present. That they are not highly malignant is shown by the presence of features which relate them to the parent thyroid tissue, such as formation of acini and colloid (Figs. 3 and 4).

Tumors in Group III, called carcinoma simplex, represent 24.6 per cent

of the cancers. Since they are the most undifferentiated and highly malignant cancers, the diagnosis is usually obvious from the clinical course, gross appearance, and histology. Microscopically, the cells are so undifferentiated that there is little attempt at even an atypical reduplication of thyroid structure. The tumors may be composed of small cells, growing in either diffuse or compact fashion, or of large cells which often resemble sarcoma as much as carcinoma in their extreme anaplasia (Figs. 5 and 6).

The tumors in the miscellaneous group make up 4.6 per cent of the total.

FIG. 1. Adenoma (papillary type) with focal invasion of capsule. Hematoxylin and eosin. ×50.

FIG. 2. Invasion of blood vessels and lymphatics. The elastica of blood vessels is accentuated by Verhoeff's elastic tissue stain. ×125.

Most appear highly malignant histologically. The incidence of lymphoid tumors is very low (0.7 per cent).

It will be noted that there is no place in the classification for cancers of "lateral aberrant thyroid tissue." Warren and Feldman (3) have recently made a careful pathologic survey of such tumors seen at this clinic and conclude that in almost every instance they represent a metastasis from a low grade cancer of the thyroid gland itself. Of utmost clinical importance is not the question of the origin of tumors from aberrant thyroid tissue, but

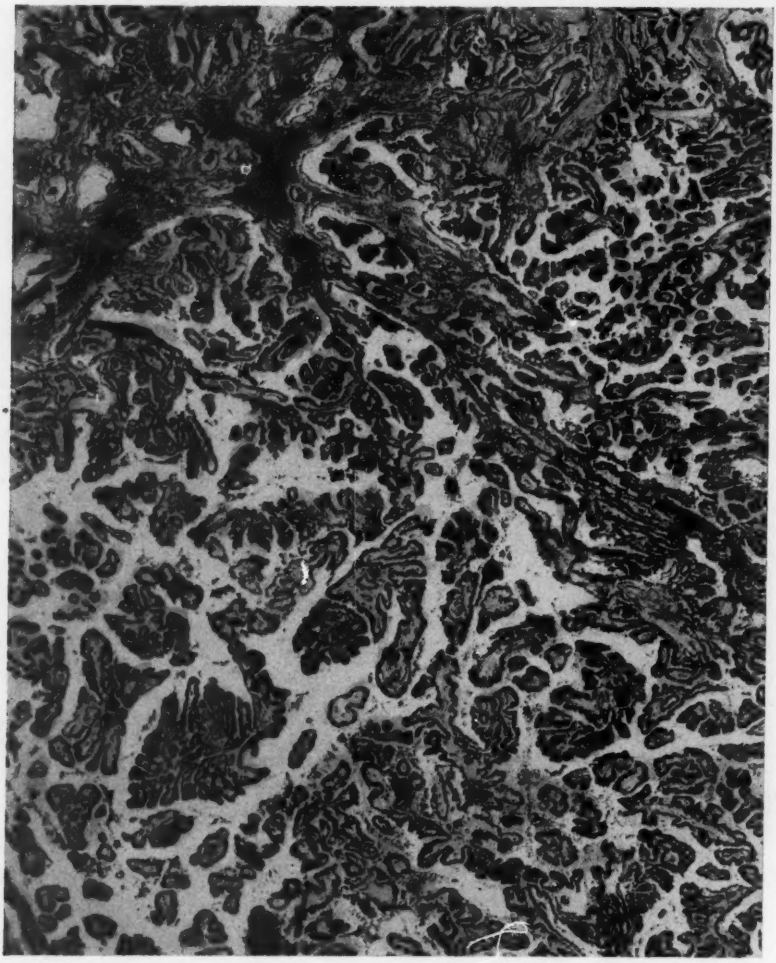

FIG. 3. Adenocarcinoma, papillary type. Hematoxylin and eosin. ×50.

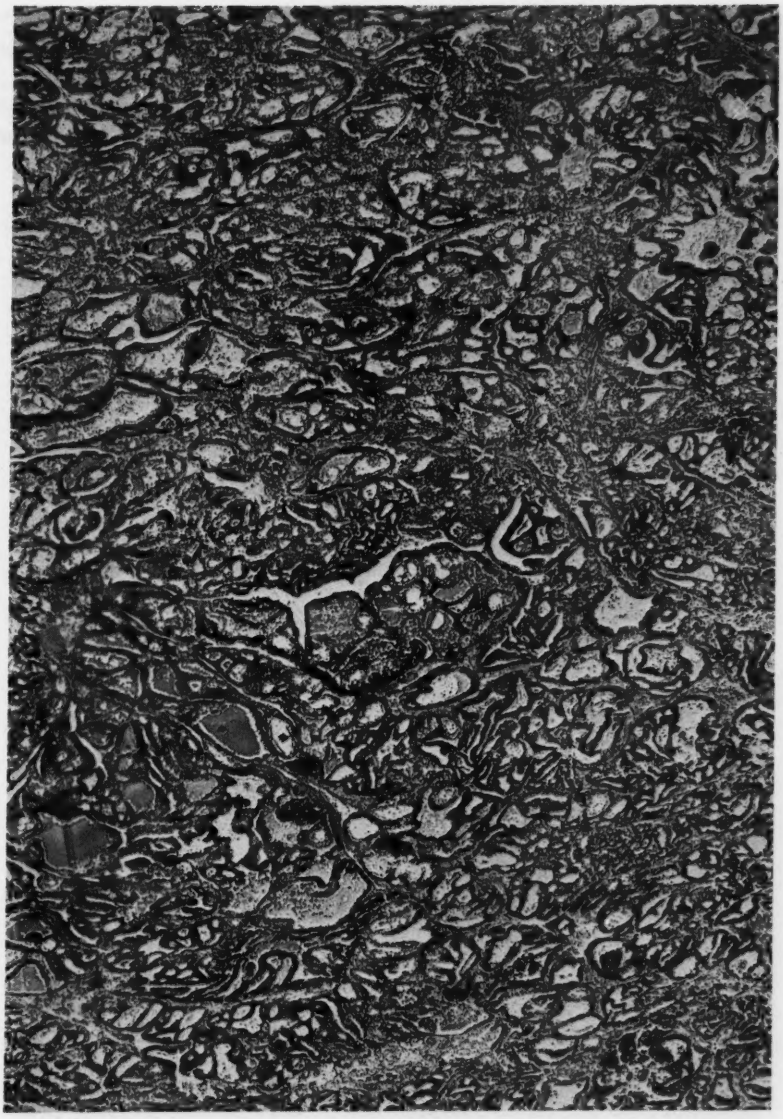

FIG. 4. Adenocarcinoma, alveolar type. Hematoxylin and eosin. ×50.

the fact that in practically every case they were able to show that a tumor was present in the corresponding lobe of the thyroid gland and that this tumor was histologically similar to that in the "aberrant thyroid tissue." This fact obligates the surgeon to remove the corresponding lobe of thyroid in every case in which such a diagnosis is considered, no matter

FIG. 5. Carcinoma simplex, small cell compact type. Hematoxylin and eosin. × 250.

whether he wishes to consider the tumors as arising in aberrant thyroid tissue or as representing metastases.

Since the surgical management of cancer of the thyroid is predicated chiefly on the pathologist's findings, it is obvious that to obtain the best results it is necessary to have close cooperation between the pathologist

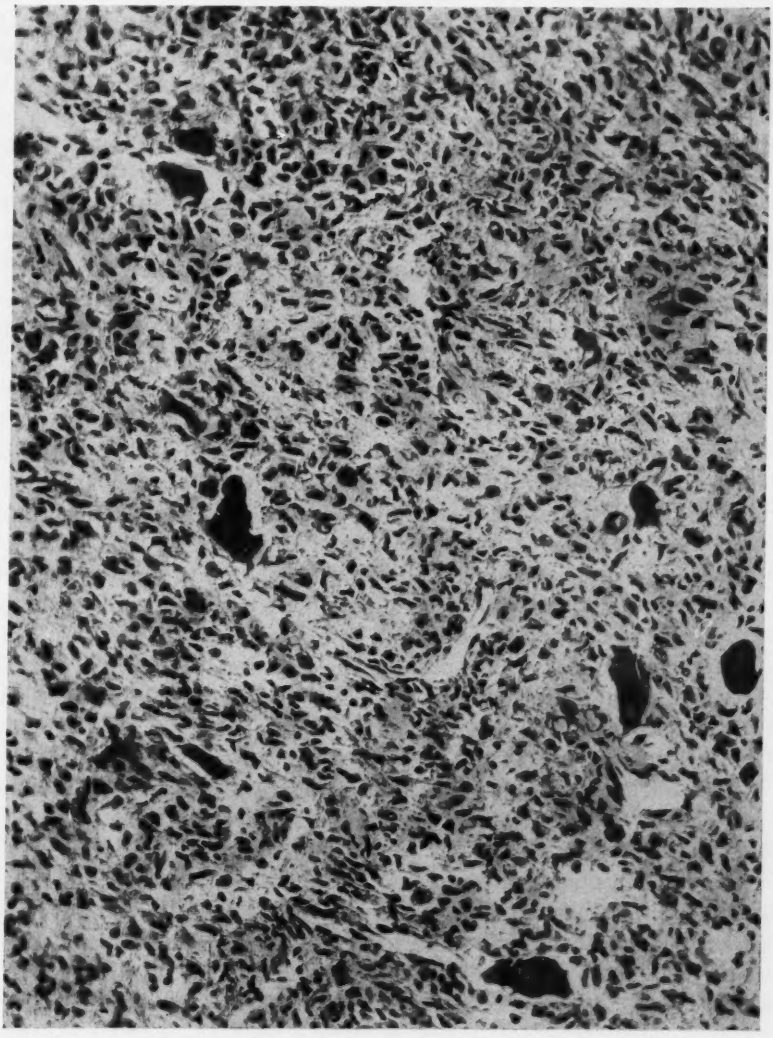

FIG. 6. Carcinoma simplex, giant cell type. Hematoxylin and eosin. × 250.

and the surgeon not only in settling whether or not the thyroid lesion is malignant but also its grade of malignancy and, very particularly, its type of invasion. Has it invaded blood vessels only? Has it invaded the capsule and lymphatics? Has it eroded the capsule and invaded the parenchyma, or have all four of these features occurred?

In considering cancer of the thyroid from the surgical point of view, three factors must be considered. What are the indications of probable malignancy in a given lesion of the thyroid; in what type must one apply radical dissection of the neck; in what type following only local removal, with the return of a pathologic report of malignancy, is it permissible to apply only radiation; and in what type is it possible to be satisfied with only local removal?

As a result of this large experience, which involves the treatment of thyroid malignancy by radical surgery when necessary, followed by intensive high voltage x-radiation, and several follow-up studies as to five-year survival rates (4, 5), we have reached certain conclusions.

The first conclusion is that we firmly believe that the incidence of thyroid malignancy arising from discrete adenomas is so real and the mortality and morbidity so low in experienced hands that all discrete adenomas of the thyroid should be removed.

It has occasionally been said by critics of this attitude that they would agree with this position if all of the adenomas could be removed by men experienced with thyroid surgery. That seems an entirely wrong approach to this problem. We must set up standards of what is the best thing to do and then the individual surgeon must approach each problem on the basis of his experience and ability to handle it. If we were to approach many of the problems of surgical treatment of malignancy on the basis of what an inexperienced surgeon might obtain in the way of mortality and morbidity figures, we would not be doing many of the operative procedures in malignancy which are opening a widening field, prolonging life and even curing patients of malignant disease.

We have tried to set up criteria as to when radical operation should be done, when it should not, and when x-radiation should follow removal of adenomas and when it need not.

In any discrete adenoma in which the only evidence of malignancy is blood vessel invasion, we do not believe that radical dissection of the neck together with removal of the lobe in which the adenoma is situated is indicated since there will be distant extension of the lesion if it occurs, because it is blood borne. It can then well be out of reach of the radical dissection or the local x-radiation. If a discrete adenoma with its capsule intact is removed and a pathologic report is returned of invasion of the capsule or lymphatic invasion, we then believe in such a case that a radical

dissection of the lymph nodes of the neck on that side, together with entire removal of the lobe in which the adenoma was present, followed by x-radiation, is indicated.

When carcinoma has eroded the capsule of the adenoma and involved the parenchyma of the gland we believe unhesitatingly that in such cases radical dissection of the neck should be carried out, together with removal of the internal jugular vein and the lobe of thyroid in which the tumor is present, and followed by intensive x-radiation.

In Group III we should place those patients with high grade cancer of the thyroid who often come to the clinic with large, fixed masses, occasionally extending into the mediastinum. We have a sufficient number of these, at first seemingly hopeless patients, alive and well to make us feel safe in saying that every attempt should be made to remove such masses as extensively as possible, endeavoring in every such case to detach the carcinomatous thyroid mass from the trachea so that that structure is not only completely relieved of pressure but also so that a tracheotomy may be instituted in it at the time of removal of the mass.

We advise the extensive removal of large and what often appears to be hopeless cancer of the thyroid, in order that the trachea may be completely freed and the tracheotomy done so that compression and obstruction will not occur during the period of extensive x-radiation therapy which must be employed postoperatively. We believe, in addition to this, that there is a distinct value to the removal of the largest possible amount of malignant thyroid mass in order to make the application of the intensive postoperative x-radiation, most effective.

CONCLUSIONS

We have presented in this paper figures of the types of cancer of the thyroid occurring in this clinic, criteria for the diagnosis of cancer of the thyroid, criteria for the classification of cancer of this type, and have discussed the indications for surgery, followed by x-radiation, in the various types. The pathologic diagnosis is of importance not only in reporting the presence of cancer, but also in assisting in the determination of the type of therapy which is to follow.

It is our opinion that the only cases of cancer of the thyroid that are utterly hopeless are those in which the masses are so extensive, so fixed, and involve such important adjacent structures that they cannot be removed so that the trachea can be freed and a tracheotomy instituted in it. When this operation can be done, followed by intensive x-radiation, there will be a surprising number of cases in which patients can have their lives prolonged for many years in comfort, and others in which cures can be brought about even in apparently hopeless cases.

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DISCUSSION

DR. FRANK H. LAHEY (Boston, Massachusetts): The cooperation between the department of Surgery and Dr. Warren and Dr. Meissner in the Department of Pathology of the New England Deaconess Hospital where all of the pathology of the clinic is done has been most gratifying. Not only have we found the cooperation of the Department of Pathology of value to us in diagnosis but we have valued their opinion also in establishing criteria for the type of operative procedures to be applied in given cases.

It is fortunate that in many of the cases of extensive cancer of the thyroid there will not be invasion of the trachea and it will be possible to separate that structure carefully from the thyroid and to institute a tracheotomy in it. It is true that there will be others in which the trachea itself will be invaded, but in our experience this has been the exception rather than the rule.

There are a few conclusions which we have reached as a result of this not inconsiderable experience with cancer of the thyroid. The first is that the carcinomas of the thyroid which are limited to one side, even though they are extensive, are more satisfactory to deal with than those which involve both sides; second, that those cancers of the thyroid in which the involvement of one side is greater than the other side, are more satisfactory to deal with than those cases in which large involvements of both lobes of the thyroid are present.

When both lobes of the thyroid are involved in malignancy it is, in our experience, much better to attempt the complete removal of only one lobe with complete freeing of the trachea and to depend upon intensive x-radiation of the remaining lobe, than to attempt the removal of both lobes. This procedure insures the preservation of one recurrent nerve and the parathyroids on one side.

One of the most important features of the surgical treatment of cancer of the thyroid, as already stated, is the complete freeing of the trachea and the institution of a tracheotomy in it in order that the swelling which

will follow the intensive x-radiation will not require an emergency tracheotomy during the period of treatment, particularly when the trachea in these extensive cases is deeply buried in malignant tissue.

There are a few warnings which we should like to give as a result of this experience. When the trachea is extensively involved in malignancy it is better to shave away most of the malignancy and leave the remnants attached to the trachea than to attempt resection of the trachea. Likewise, when the malignancy involves the esophagus, which it so frequently does along its lateral wall, it is better to leave small strips of malignant tissue attached to the esophagus and to depend on x-radiation for its management, than to attempt resection of the esophagus.

We have learned that when malignancy of the thyroid has extended into the mediastinum and is fixed there, attempts to dissect it out of the mediastinum are futile; that they will be followed only by excessive bleeding requiring packing, and the establishment of hematomas. In such cases in which the malignancy is extensive, it has been our experience that it is better not to attempt such removal. When, however, malignant masses that are movable extend beneath the clavicle, they can frequently be mobilized, delivered and removed.

The criteria of the occurrence of malignancy have been discussed and are well known by everyone dealing with thyroid disease. They are: fixation of the thyroid mass, a marble-like consistency, and particularly irregularity and nodularity of a firm character with the loss of thyroid outline. While recurrent laryngeal paralysis, particularly when associated with a firm and fixed tumor, should lead one to suspect the possible presence of malignant degeneration in a thyroid adenoma, we have frequently been surprised by the maintenance of good vocal cord motion in spite of the presence of extensive thyroid malignant degeneration.

In the diagnosis of thyroid malignancy there is no other disease which creates a greater suspicion of cancer of the thyroid than thyroiditis. The outstanding features of thyroiditis are firmness and fixation. The firmness is often of similar hardness and comparable to that which is not infrequently seen in malignancy. A differentiating point, however, between thyroiditis and cancer of the thyroid is that thyroiditis is an inflammatory infiltration either of one entire lobe or of both lobes and the isthmus. This infiltration, while it not infrequently enlarges one lobe more than the other, practically never results in a loss of the anatomical outline of the thyroid gland. There is still an apex to the upper pole; there is still a definite lateral lobe and body and a definite isthmus. This has been, in our experience, one of the most valuable differentiating points between malignancy and the lesion which often so closely simulates it—thyroiditis.

CARCINOMA OF THE THYROID GLAND, WITH SPECIAL REFERENCE TO A CLINICO-PATHOLOGIC CLASSIFICATION*

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CLINICAL ASPECTS

FROM the clinical point of view carcinomas of the thyroid can be divided into two main groups, the papillary and the nonpapillary. Papillary carcinomas behave as lymphangioinvasive tumors and metastasize to lymph nodes, whereas nonpapillary carcinomas are hemangioinvasive and metastasize through the blood stream. The great differences in the clinical behavior and prognosis of these two groups of tumors can be explained by their respective tendencies to invade lymphatics and blood vessels.

Papillary carcinomas tend to be nonencapsulated, or at least nonenucleable. If a capsule is present it is formed by sclerosis and is densely adherent to the surrounding thyroid tissue so that it cannot be "shelled out" like the differentiated nonpapillary carcinomas. It is perhaps because the papillary carcinomas originate in the parenchyma of the thyroid, which is well supplied with lymphatic vessels, that they tend to invade lymphatics. If the nonpapillary tumors arise in adenomas the absence or paucity of lymphatics in these adenomas may explain their tendency to invade blood vessels rather than lymphatics.

Papillary tumors of the commonly recognized type occur frequently in children and young adults, whereas nonpapillary tumors follow more closely the general age distribution of most other carcinomas. This tendency to occur in the young cannot fail to suggest the possibility that papillary carcinomas arise in congenital rests and are not related to the presence of endemic goiter, whereas nonpapillary carcinomas may arise more often in adenomas, tend to be more common in regions of endemic goiter, and are diminishing in frequency as goiter becomes less common.

Papillary carcinomas carry a much more favorable prognosis than nonpapillary carcinomas and, even when there is extensive metastasis to regional lymph nodes, cures usually are effected by removal of the tumor and the metastatic nodules. When nonpapillary tumors metastasize to lymph nodes the prognosis usually is hopeless.

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More than twenty years ago Dr. Allen Graham recognized these fundamental differences between the papillary and nonpapillary tumors of the thyroid, and he named the nonpapillary tumors "malignant adenomas." This term stemmed from his belief that the nonpapillary tumors originated in adenomas and became malignant. All such tumors, whether highly differentiated angioinvasive adenomas or undifferentiated carcinomas, he classified as malignant adenomas, a term which was misunderstood because the word "adenoma" implied a benign quality which the term as used by Graham did not signify. Hence we have modified Graham's classification, renaming the malignant adenoma "nonpapillary carcinoma" (Table 1).

TABLE 1. COMPARISON OF CHARACTERISTICS OF PAPILLARY AND NONPAPILLARY CARCINOMAS

	Papillary Carcinoma	Nonpapillary Carcinoma
Origin	? Congenital rest	? In an adenoma
	Probably no relationship to endemic goiter	Relationship to endemic goiter
Incidence	Children and young adults	Adults and aged
Encapsulation	Absent or poor	Enucleable until capsule is invaded by tumor
Behavior	Lymphangioinvasive. Metastasis to lymph nodes	Hemangioinvasive. Metastasis through blood stream
Prognosis	Good, if locally removable	Fair to poor, depending on degree of anaplasia

The classification retains Graham's two great groups: 1) the lymphangioinvasive papillary carcinomas which are nonencapsulated or at least nonenucleable, occur in young people possibly as congenital rests, invade lymphatics, and metastasize to the regional lymph nodes; and 2) the hemangioinvasive nonpapillary tumors which, if they originate in adenomas, are encapsulated and enucleable until the capsule is invaded, occur in an older age group, invade blood vessels, metastasize distantly through the blood stream, and carry a much graver prognosis.

In addition to the more common papillary and nonpapillary tumors, it was found necessary to designate another group as special types, including squamous cell carcinoma, metastatic carcinoma and a third unusual lesion, nonencapsulated sclerosing tumor (Table 2). This last type is classified by

Graham as adenocarcinoma not originating in adenoma and by Goetsch as carcinoma of the hyperplastic thyroid. These tumors are small, rarely exceeding 2 cm. in diameter and are usually incidental findings in the course of a thyroidectomy done for other causes. They are of questionable malignancy, hence are designated as nonencapsulated sclerosing tumors rather than carcinoma. It is quite possible they should not be included among the malignant tumors of the thyroid gland.

TABLE 2. CLASSIFICATION OF MALIGNANT TUMORS OF THE THYROID

A. Carcinoma
  I. Papillary carcinoma
  II. Nonpapillary carcinoma
    a. angioinvasive adenoma
    b. adenocarcinoma
    c. undifferentiated carcinoma
  III. Special types
    a. nonencapsulated sclerosing tumor
    b. squamous cell carcinoma
    c. metastatic carcinoma

B. Sarcoma
  I. Lymphoma
  II. Spindle cell sarcoma

PATHOLOGIC ASPECTS

The presentation is based upon a detailed study of thyroid carcinomas removed from 60 patients during the decade from 1936 to 1945. These epithelial tumors were classified as follows: papillary carcinoma, 34 or 56 per cent; nonpapillary carcinoma, 22 or 37 per cent; special types 4 or 7 per cent.

The papillary group presented several interesting histologic variants. The majority, 19, were classified as typical cystic or adenocarcinoma variants, the more solid or cystic morphology depending often upon the particular area examined. Distinct histologically was a tall-cell type of papillary tumor, the cells being columnar, 15 to 25 microns in height and slightly more oxyphilic than usual. Six of the papillary tumors showed this type of cell. These tend to be bulky tumors and occur in an older age group. Three additional papillary neoplasms were of similar morphology but in addition to the distinctive appearance of the epithelium, showed a dense infiltration of stroma by lymphocytes. A third unusual variant, of which 6 examples were encountered, was comprised of well differentiated epithelial cells for the most part in medullary arrangement but with some papillary areas.

Gross encapsulation was noted in 12 of the 34 papillary neoplasms but all showed variable degrees of capsular invasion microscopically and could not be regarded as enucleable. Eighteen of the papillary tumors were associated with lateral nodules. Blood vessel invasion was established in only one instance.

The 22 carcinomas of the nonpapillary group included angioinvasive adenoma 3, adenocarcinoma 8 and undifferentiated carcinoma 11. Encapsulation was noted in the angioinvasive adenomas and partial encapsulation in the adenocarcinomas. The majority of the undifferentiated carcinomas were diagnosed by biopsy; in the few in which the whole specimen was available no encapsulation was observed. Blood vessel invasion was a common feature of the nonpapillary group. Two of the adenocarcinomas were oxyphilic or so-called Hürthle cell carcinomas.

Of the special types, 1 was a squamous cell carcinoma and 3 were nonencapsulated sclerosing tumors. The squamous cell carcinoma was of classic histologic appearance. The nonencapsulated sclerosing tumors were of small size, varying from 8 to 20 mm., hard, white and found incidentally in hyperplastic, colloid, and nodular goiters. Histologically they presented an adenopapilliferous architecture with abundant dense stroma.

Except for metastatic carcinoma, examples of all groups were found in the present series. On anatomic bases, the papillary group had several variants, noted previously and designated as cystic, adenocarcinoma, tall-cell, tall-cell with lymphocyte infiltration, and medullary. With the exception of the cystic and adenocarcinoma variants there was not available in this series a sufficient number in these subgroups to allow conclusive evaluation of the clinical course.

Though a few of the cases were too recent for a definitive follow-up, there were certain significant prognostic variations. Of the 34 instances in the papillary group, the 3 patients who died of the disease had neoplasms of the tall-cell variant. Two of the patients were living with recurrences. In the nonpapillary group,11 of 17 patients died, the survivals including 2 patients with angioinvasive adenomas. Of the special types, only the 3 patients with nonencapsulated sclerosing tumor survived.

During the decade concerned in the review, 4 sarcomas were encountered including 3 lymphosarcomas and 1 spindle cell neoplasm, a fibrosarcoma. These will not be discussed.

In conclusion, an attempt has been made to present a classification of malignant tumors of the thyroid which it is hoped retains the logic of Graham's classification, divides the common thyroid neoplasms into the two major clinical groups and yet retains basic pathologic nomenclature.

APPRAISAL OF THE GOITROGENS*

RESULTS OF TREATMENT WITH THIOURACIL, PROPYLTHIOURACIL AND RELATED ANTITHYROID DRUGS

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IT IS five years this May since Astwood (1) first reported on the treatment of hyperthyroidism with thiouracil. This monumental development did not go unheeded; since then reports by numerous observers have appeared in the literature throughout the world, all confirming the fact that this drug and its derivatives exert a specific ameliorating effect on clinical hyperthyroidism. Sufficient time has elapsed to permit evaluation of the role these new potent therapeutic agents can play in the treatment of hyperthyroidism. It is with this latter aspect that I wish to deal, reviewing particularly the experience at the Lahey Clinic in treating over 1300 patients with hyperthyroidism.

Thiouracil which at first was used extensively in this country has been practically replaced by propylthiouracil, another drug introduced by Astwood (2). Thiourea received thorough clinical trial by Peters and his co-workers (3) at Yale with favorable results. An increasing number of reports are now being made on the clinical use of methylthiouracil. This contribution to the search for an active antithyroid substance was suggested by Jensen of Denmark in 1944, and has been used widely in Denmark, Sweden and Norway. Chapman (4) and O'Donovan (5), without knowledge of the Danish investigation, used the same drug in England and additional reports on its use have been published in that country (6–9). Poate and his co-workers (10) in Australia have used both thiouracil and methylthiouracil. In this country, only a few articles (11–13) on the use of methylthiouracil have appeared. Aminothiazole was used in France and England but was not given wide clinical trial by American investigators. Thiobarbital (14) received only brief trial; because of the high incidence of reactions its use was quickly abandoned.

ACTION

The antithyroid drugs have a specific action in preventing the formation of thyroid hormone. Their administration to a patient with hyperthyroidism results in gradual relief of hyperthyroid signs and symptoms, with a

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fall in the basal metabolic rate, lowering of the blood iodine level and a decrease in the iodine content of the thyroid gland. At first it was thought that this action resulted from a physiologic barrier to the absorption of iodide by the thyroid gland. Clinical experience, however, proved this invalid since the administration of Lugol's solution to patients receiving an effective dose of the antithyroid agent was observed to result in involutional changes in the thyroid gland. Our study of the iodine content of the thyroid glands of patients who had hyperthyroidism and were receiving antithyroid treatment revealed that the gland of those patients given added Lugol's solution contained larger amounts of stored iodine than did those of patients who received only the antithyroid drug. McGinty (15) clarified the problem by finding that the iodine stored in the rat treated with antithyroid agents following the giving of Lugol's solution was entirely inorganic in form. This forced the conclusion that the antithyroid drugs act by preventing the synthesis of organic iodine from the inorganic form. A recent report by Stanley and Astwood (16) confirmed the finding that iodine was absorbed by the thyroid following antithyroid treatment. They found that appreciable quantities of radioactive iodine, which is in the iodide ion, are absorbed by the human thyroid even after complete inhibition of synthesis of thyroid hormone by antithyroid medication. At this meeting last year, De Robertis (17) indicated that the goitrogens act by direct interference with the peroxidase or enzymatic system in the thyroid gland which is involved in the synthesis of the organic thyroid fraction from stored inorganic iodine (iodide).

The comparative amounts of inorganic and organic iodine present in the thyroid gland under various conditions is diagrammatically shown in Figure 1, A to D. In the normal gland most of the iodine is stored as organic iodine (A). In hyperthyroidism, there is a fall in the organic fraction and a slight increase in the inorganic fraction; these changes result from a rapid loss of organic iodine from the thyroid gland and greater uptake of iodide due to an increase in availability (B). As the disease progresses there is a decline in both iodine fractions. Under antithyroid treatment (C) there is a marked decrease in organic iodine owing to suppression of production of the hormone containing organic iodine; iodine is absorbed but not utilized. When Lugol's solution is given after antithyroid therapy has inhibited synthesis of organic iodine, there is a marked increase in the inorganic iodine but the organic iodine remains low in amount (D).

UNIFORMITY OF ACTION

It has been our experience that no patient with hyperthyroidism will fail to respond to the goitrogens if a suitable dose is given over a sufficient length of time. Should adequate antithyroid therapy fail to ameliorate the

patient's symptoms one is forced to conclude that the diagnosis of hyperthyroidism is in error and some other cause for the patient's symptoms must be found.

There have been reports (18–20) regarding the failure of the goitrogens to reduce the elevated metabolic rate of acromegaly. Only if the patient with acromegaly has associated hyperthyroidism can one expect a lowering of the rate under treatment and then not to a normal level since patients with acromegaly without goiter may have an elevated metabolic rate. In 2

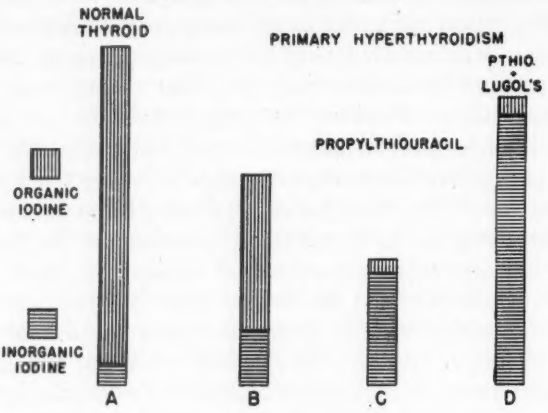

FIG. 1

cases of acromegaly with goiter in which the patients were given prolonged antithyroid treatment there was striking clinical improvement. There was a gain in weight of 25 pounds in each case. The metabolic rate of the first patient dropped from plus 65 to plus 26, and that of the second patient from plus 63 to plus 39 after six months of treatment. Both patients had a subtotal thyroidectomy and in each a large adenomatous goiter was removed; one weighed 250 Gm. and the other, 88 Gm. Three months after operation the metabolic rates were practically the same as before operation, plus 24 and plus 33 respectively. Since this residual elevation of metabolic rate is attributed to pituitary disorder, one could not expect it to be affected by any amount of antithyroid therapy. If acromegaly is associated with hyperthyroidism, as in these 2 cases, improvement will follow treatment but the metabolic rate will not fall to the normal range.

DOSAGE OF ANTITHYROID DRUGS

The dose of thiouracil first employed was 600 mg. a day. The average dose of propylthiouracil is 200 mg. daily but 300 mg. is the usual dose for

cases of adenomatous goiter or cases of primary hyperthyroidism with large goiters.

We are now gaining experience with the use of methylthiouracil. A daily dose of 300 mg. produces a favorable response in all patients. In some patients the response exceeded that which would be expected to follow the administration of 200 to 300 mg. of propylthiouracil. The present plan is to give methylthiouracil in the same dosage as propylthiouracil, that is 200 mg. daily to patients with primary hyperthyroidism who have only moderate-sized goiters and 300 mg. daily to patients with large goiters due to either primary hyperthyroidism or adenomatous goiter. To date, 40 patients have been treated with methylthiouracil, with satisfactory results.

REACTION TO GOITROGENS

The incidence of reactions to thiouracil has uniformly been reported to be about 10 per cent. Propylthiouracil causes reactions much less often. So few and so slight were the reactions among the first 100 patients treated by Astwood and Vanderlaan (2) that the impression was gained that this drug is entirely void of side effects and therefore could be given without the

TABLE 1. REACTIONS TO PROPYLTHIOURACIL

Type of Reaction	Number of Reactions
A. White blood cell depression. Agranulocytosis	3
Granulocytopenia or leukopenia	7
B. Fever	3
C. Skin eruption	1
D. Edema of skin	1
Total reactions (patients treated, 820)	15
Reaction incidence	1.8%

precautions required with thiouracil therapy. This optimism has not been justified by later experience. Eight reports (19) dealing with the use of propylthiouracil indicate agranulocytosis to have occurred twice, granulocytopenia sufficient to warrant withdrawal of treatment occurred in 2 patients, generalized rash in 2, urticaria in 3 and fever in 1 patient. Numbness of the extremities, nausea and arthralgia were also noted. Among these 486 reported cases there were 11 reactions, an incidence of 2 per cent. At the Lahey Clinic, 820 patients have received propylthiouracil. Fifteen definite reactions were observed, a reaction incidence of 1.8 per cent (Table 1). Since 10 of the reactions involved the blood, with 3 leading

to agranulocytosis, it must be concluded that propylthiouracil cannot be given without danger and that it must be administered under careful supervision if serious complications are to be avoided.

In a recent report, Barfred (20) reviewed the experience of the European workers with the use of methylthiouracil. Among 604 cases from 18 authors there was a 7 per cent incidence of reactions and 9 of the patients had agranulocytosis. This incidence of agranulocytosis, 1.49 per cent, is similar to that reported by Moore (21) following thiouracil, 1.74 per cent. Crile (11) and McCullagh (18) reported no reactions in treating 24 patients with methylthiouracil in doses up to 400 mg. daily. Poate (10) of Australia treated 84 patients, with 7 reactions, in which marked degrees of leukopenia occurred in 2 patients. In 28 of his 84 patients the leukocyte count fell from 1000 to 2000 cells during treatment. This and other reports mentioned that mild dermatitis, drug fever, leukopenia, conjunctivitis, exfoliative dermatitis, cervical adenitis and effusion of fluid in the joints accompanied the use of methylthiouracil. Our experience with this latter drug consists of treating 40 patients; 5 patients had reactions. Four patients developed a skin rash; in 2 the rash was severe and in all, treatment had to be discontinued. Two of these patients were then able to take propylthiouracil without difficulty. One patient who developed leukopenia from propylthiouracil had a similar change in the blood following methylthiouracil. One patient who had fever after taking propylthiouracil took methylthiouracil without difficulty. One patient who was skin sensitive to propylthiouracil was also skin sensitive to methylthiouracil. We have not treated a sufficient number of patients with methylthiouracil to give a final opinion regarding its toxicity but predict it will be higher than that of propylthiouracil.

CLINICAL USE OF THE GOITROGENS

A. Preoperative therapy

The inestimable value of the antithyroid drugs in preparation for surgery has been firmly established. Treatment must be continued until a euthyroid state is obtained and in some patients maintenance therapy must be continued for months before thyroidectomy can be safely undertaken. Full control is strongly urged before operation is undertaken since those having wide experience with hyperthyroid patients are well acquainted with their unpredictableness. Serious anesthesia and postoperative reactions occasionally occur in patients with primary hyperthyroidism even when the basal metabolic rate is only slightly elevated. However, when the patient is euthyroid, a smooth course is assured in the operating room and afterward.

As important as full control of hyperthyroidism preoperatively is the avoidance of overtreatment with antithyroid drugs, which can result in myxedema. Since myxedema is associated with morphine sensitivity, an average dose of morphine postoperatively will cause a depression of the respiratory rate and cough reflex which may lead to serious pulmonary complications. Therefore, patients presenting minus basal metabolic rates must be carefully observed from the standpoint of myxedema before proceeding with thyroidectomy. It has been observed repeatedly that in patients treated with the antithyroid agents the blood cholesterol may be in the myxedematous range without obvious signs of myxedema or a greatly reduced basal rate. It is necessary, therefore, that myxedema be considered in all patients with minus metabolic rates. If it is present, the operation should be delayed until the metabolic rate and blood cholesterol have returned to normal.

Some observers have disagreed with our reported prediction rate of the decline in metabolic rate during antithyroid treatment. Continued experience has shown that although there may be an occasional exception, the basal metabolic rate in cases of primary hyperthyroidism falls at the rate of 1 per cent for each day of treatment and in adenomatous goiter, 0.5 per cent per day.

It has been found advisable to give Lugol's solution to patients with primary hyperthyroidism prior to thyroidectomy. Initially, we suggested that Lugol's solution be given during the last three weeks of treatment. Last year we suggested that it be given concurrently with the antithyroid drug as a means of producing more rapid improvement, although there was a delay in the ultimate return of the metabolic rate to normal. We now suggest, except for patients in crisis or near crisis states who need immediate administration of iodine, that iodine be given according to the initial plan, administering it during the last three weeks of preoperative treatment. This change in policy in the administration of iodine became necessary when it was found that some patients with large goiters required a greatly prolonged course of treatment if iodine was started at the beginning of the course.

The benefits derived from proper antithyroid treatment preoperatively are readily apparent, since operations in two or more stages which were previously done in 8 to 12 per cent of cases have now been completely eliminated and operative mortality has been drastically reduced—one death occurred in 1240 consecutive cases, a mortality rate of 0.08 per cent. This very low mortality rate gains added significance when it is realized that no patient, irrespective of age or condition prior to antithyroid treatment, was refused thyroidectomy.

B. Medical therapy

It is generally agreed that hyperthyroidism resulting from either primary hyperthyroidism or adenomatous goiter can be completely controlled and maintained under control as long as an adequate dose of an antithyroid drug is administered. A wide divergence of opinion exists, however, as to:

1) The incidence and duration of remission after withdrawal of antithyroid treatment and the length of time treatment is necessary in attempting to start a remission.

2) The advisability of prolonged or maintained treatment should a remission fail to follow a reasonable course of adequate treatment.

The reported incidence of remissions after treatment shows wide variations. Some observers report remission in as high as 80 per cent of cases and others in as low as 20 per cent, with the remissions varying from a few months to two years. That no satisfactory criteria exist to judge the duration of treatment required to produce a prolonged remission is indicated by the fact that six months has been suggested by some and as long as one and a half years by others. In spite of long periods of treatment, patients cannot be assured that they will remain well. Some patients have a remission after only short periods of treatment; these are usually patients with mild hyperthyroidism who have small hyperplastic goiters. Actually, a longer period of careful observation will be needed to determine whether the remissions which are produced are of sufficient length to be worth while attempting to accomplish.

Should prolonged remission or cure consistently follow the withdrawal of antithyroid treatment, those interested in the therapy of hyperthyroidism would welcome its use in certain patients. It is when prolonged or maintenance treatment becomes necessary that a cleavage of opinion develops and arguments arise as to the advantages of maintenance antithyroid over surgical treatment of hyperthyroidism (Fig. 2). The advantage of medical treatment is, of course, the avoidance of a thyroidectomy and its possible postoperative complications. The disadvantages or objections to prolonged medical treatment are many. Continuous treatment indicates that there is no hope of permanent cure. In no instance have we observed the goiter to decrease in size with therapy but it is not uncommon to note an increase in size which, at times, is considerable. Most experienced clinicians are in accord with the general policy of removing all adenomatous goiters because of the risk of malignant disease and of pressure on other structures in the neck. Although the reaction incident to propylthiouracil is small (2 per cent), there is always the pos-

sibility of leukopenia which, if allowed to go untreated, may lead to a fatal outcome.

Whether significant histopathologic change will follow prolonged antithyroid treatment still remains to be answered. Among the 1200 goiters which were removed following antithyroid treatment, 7 were reported to show malignant change. Three of these were in adenomatous goiters and 4 in primary hyperthyroid goiters. This finding of 7 carcinomas in 1200 cases of hyperthyroidism must be carefully compared with the incidence

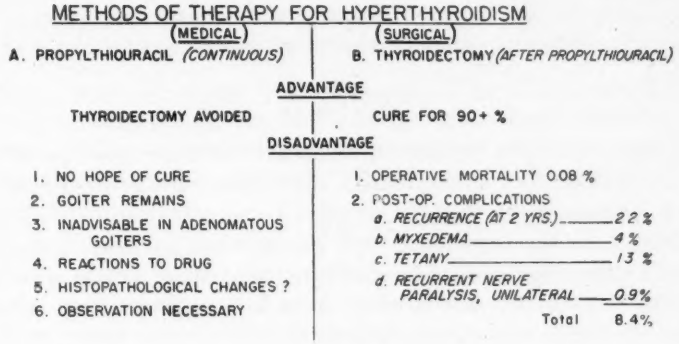

FIG. 2

before using antithyroid drugs before its actual significance is determined. The finding of malignant change in 4 primary hyperthyroid goiters strongly emphasizes the fact that even this type of goiter is best removed.

Prolonged or maintenance therapy is frequently difficult since repeated observations are not always possible because of poor cooperation of the patient. When patients improve, treatment may be allowed to lapse, with a return of hyperthyroidism, and many times this occurs in patients who can ill afford it. We are seeing an increasing number of patients who have tried prolonged antithyroid treatment with its problems, who now prefer to have their problem settled by thyroidectomy.

Thyroidectomy after proper antithyroid control of hyperthyroidism results in permanent and complete return to health in over 90 per cent of cases. The danger of operative mortality has practically been abolished, as indicated by 1 death in 1240 cases. There *are* certain definite postoperative complications, but only parathyroid tetany, which occurs in 1.3 per cent of cases, represents a real problem. Myxedema, which occurs in 4 per cent of the cases, is completely controlled by inexpensive and simple treatment with desiccated thyroid. In a way, myxedema may actually be welcome

since it practically eliminates the chances of recurrent hyperthyroidism. Recurrent hyperthyroidism occurred in 2.2 per cent of the patients whose course was followed up to two years; one half of these patients are being controlled by a maintenance dose of Lugol's solution and the other one half underwent further thyroid removal. Unilateral recurrent nerve paralysis was very infrequent and is not a serious problem since it leaves the patient with only minor hoarseness which is not hazardous.

Thyroidectomy shortens the time of complete recovery from hyperthyroidism, for most patients are entirely well and over the effects of thyroidectomy in two or three months. Much more time is required for recovery of health when medical treatment using the antithyroid drugs is employed.

SUMMARY

Five years have now elapsed since Astwood's first report on the use of thiouracil in clinical hyperthyroidism. Since then various other antithyroid agents have been given trial. In addition to reports on thiouracil, reports are available on the experience with propylthiouracil and more recently with methylthiouracil. All observers agree that these agents alleviate the symptoms of hyperthyroidism when given in a sufficient dose. That their action is specific in preventing the formation of organic iodine or thyroxin from inorganic iodine has been firmly established. The effective dose of thiouracil, propylthiouracil and methylthiouracil is 600 mg., 200 to 300 mg. and 200 to 300 mg., respectively. The incidence of toxic reactions is 9 per cent for thiouracil, 2 per cent for propylthiouracil and approximately 10 per cent for methylthiouracil.

All investigators are in entire agreement as to the great benefit of these drugs as preoperative adjuvants. Difference of opinion has existed regarding their value as substitutes for surgery, but this hope is waning. Mild primary hyperthyroidism may lapse into a prolonged remission after a course of treatment, but in severe primary hyperthyroidism with marked enlargement of the thyroid, treatment must be combined for control and this carries with it many disadvantages. Almost all observers agree that patients with adenomatous goiters are not suitable for prolonged treatment.

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CERTAIN GOITER PROBLEMS*

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THE thyroid gland has probably been the subject of more intensive study than that of any other organ. The operative technique for thyroidectomy has been more completely standardized than for any other major surgical procedure.

Most of the great advances in the recognition and treatment of diseases of the thyroid have been made by men with whom most of us have had the pleasure and privilege of working or the opportunity of observing their work—Kocher, Horsley, the Mayos, Crile, Plummer, and many of our own members still actively engaged in practice. However, there remain certain problems that must be clarified.

Many patients with long standing low grade chronic hyperthyroidism are still being overlooked. Thyrocardiacs are not being recognized early enough. The incidence of carcinoma of the thyroid and the necessity for early recognition of it and the proper surgical measures to be adopted must be impressed not only on the medical profession, but on the laity as well.

GOITROGENIC DRUGS

The value of powerful goitrogenic drugs, their safety and ill effects should soon be determined. The intense enthusiasm with which they were received by many has waned, and it is probable that their greatest value will be in patients with hyperthyroidism who do not respond to iodine, or at least not quickly enough, in recurrent exophthalmic goiter, and perhaps in that very small percentage of toxic adenomatous goiters in whom, for one reason or another surgery is not warranted. Up to the time of the Atlanta meeting last year, Cope reported 27 collected cases of death due to the use of goitrogenic drugs. Perhaps the total deaths up to date will be presented at this meeting. This is too high a mortality and must be materially reduced if such drugs are to be used. The value of that wonder drug, penicillin, in combatting the ill effects of the goitrogenic drugs has been demonstrated, but further study and experience must develop a goitrogenic substance that does not cause leukopenia or agranulocytosis. To my mind, such a drug will be developed, and could revolutionize particularly the treatment of exophthalmic goiter, but I do not believe it can

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be expected to offset or replace the necessity for surgery in tumorous goiters.

The recent report of Mulholland, Lawler and Ralli of the Third Division, Bellevue Hospital on the value of intravenous sulfadiazine administered preoperatively and postoperatively in offsetting a hyperthyroid storm, is very interesting and warrants further investigation of its value.

RADIOACTIVE IODINE

In 1934 radioactive iodine was prepared by Fermi. Since then a small group of investigators used it to study the physiology of the thyroid gland. It is only in the last three years that it has been employed in the treatment of exophthalmic goiter to any extent, and in the last two years in the treatment of malignant thyroids. Since the radioactive isotope I^{131} with a half-life of eight days has become available it has been much more widely used, and with encouraging results.

From the patient's point of view, radioactive iodine has much to recommend it. The entire dose is given orally in a glass of water. There are no immediate ill effects except a little nausea when the dose has been higher than usual.

It seems that sufficient radioactivity may be stored in an exophthalmic goiter to induce remissions in a high percentage of such patients, and it has proved to be of some value in perhaps 15 per cent of carcinomas of the gland. A few failures in the control of hyperthyroidism have occurred, and unfortunately myxedema has resulted in a few patients.

A tracer dose of radioactive iodine promises to be of great value in locating thyroid tissue in atypical positions. The dosage is still unsettled. No grave ill effects have been reported in liver or kidney function, but much basic investigation must be done on the possible ill effects on the other endocrine glands.

This latest therapeutic agent in the control of hyperthyroidism is very promising, and every effort should be made to establish the values and dangers, if any, of its use.

Efficiency in distribution of the radioactive isotopes, methods of handling it and the expense to the patient should be determined as soon as possible so that its widespread use will not be unduly delayed.

SURGERY

Fibrillation: We still see patients with extremely toxic exophthalmic goiter, although not as many as in former years. There is a definite percentage of them with great weight loss, heat intolerance, intense tremor diarrhea, vomiting, well-marked exophthalmos, a heart racing at the rate

of perhaps 160 or 170, and yet no fibrillation. On the other hand, fibrillation occurs very frequently in toxic adenomatous goiter. A patient may have a single small degenerating adenoma but a fibrillating heart. Removal of the adenoma clears up the fibrillation almost miraculously. What is it in that degenerating adenoma that causes such a grave complication so constantly? The isolation of that extremely toxic agent might do away with even the small mortality that persists to plague us in surgery of toxic adenomatous goiters.

Preoperative preparation: Physicians still tend to depend too much on the basal metabolism test as evidence of the presence, and even of the severity, of hyperthyroidism. A single test, and even a mean average of several tests, is probably the least reliable of all evidence as to the degree of toxicity. Tachycardia, fibrillation, weight loss, the age of the patient, duration of the disease, general fatigue, weakness, heat intolerance, the degree of exophthalmos, and tremor are vastly more accurate indications of the gravity of the disease. The response to rest, high caloric diet, iodine administration, perhaps propylthiouracil, calcium, phosphorus, glucose, amino acids and such, is the most important indication as to when surgery can most safely be undertaken, and just how much should be done.

Cancer of the thyroid: The incidence and types of cancer of the thyroid were uncertain and obscure until recent years due largely to insufficient criteria for the pathological diagnosis of malignancy. Thanks to the great contribution of Allen Graham in recognizing that vascular invasion was constant in carcinoma of the thyroid, and the work of Broders and other contemporary pathologists, the difficulties in pathologic diagnosis and grouping of malignancy of the thyroid have been cleared up. Unfortunately, it has not been an easy matter to go back over the thousands of goiters in storage and determine in them accurately the incidence of carcinoma. In the last few years, the pathologic picture has been standardized and the frequency and types of malignancy can be clearly determined. Probably 91 to 93 per cent of carcinomas of the thyroid occur in adenomatous goiters. Carcinomas do not occur in pure exophthalmic goiters. A small number have been reported in exophthalmic goiters, but have been found to occur in adenomatous cell rests within the substance of the gland. Approximately 3 per cent of adenomatous goiters have been found to be carcinomatous.

There is still too wide a variation in the incidence of malignancy reported in groups of solitary adenoma—from less than 2 per cent to as high as 27 per cent. It is important that the relatively high incidence of carcinoma found in solitary tumors of the thyroid should be accurately determined. However, there is sufficient evidence to warrant subtotal thyroidectomy in experienced hands of all adenomatous goiters regardless of the possibility

of toxicity, pressure symptoms, or of the gland assuming a low substernal position.

Aberrant thyroids: For too long, lateral aberrant thyroid nodules were overlooked. It is difficult to explain this curious oversight. Perhaps lack of a clear appreciation of the embryologic development of these nodules accounts for it. It was first brought to my attention in the Wilm's Clinic in Heidelberg in 1913. The discrete, gland-like bodies occurring in the neck medial to and just under the anterior border of the sternomastoid were mistaken for ordinary glands. Even the finding of carcinoma in one of the glands removed for biopsy was too often looked upon as metastasis, and later the discovery of papilliferous carcinoma in the adjacent lobe of the thyroid was interpreted as metastasis from the glands to the thyroid. It is now generally realized that the growth starts in the thyroid and spreads to the lateral masses. A complete block dissection of the nodules from the mastoids to the clavicles and a wide resection of the involved lobe of the thyroid should be carried out promptly, followed by x-ray therapy. It is usually sufficient to remove the adjacent lobe of the thyroid and the isthmus as well as the nodes.

Clinical diagnosis is usually not difficult. The condition must be distinguished from simple tumors, branchial-cleft cysts, carotid body tumors, neurofibromas, tuberculosis, Hodgkin's disease, lymphosarcoma, metastatic carcinoma and inflammatory glands. Biopsy should at once be undertaken. The pathologic picture of papillary cystadenomatous structure confirms the diagnosis.

Anesthesia: A select anesthesia has an important role in reducing mortality, simplifying operation, and in eliminating the dread of the anesthesia, which is so often greater than the fear of the operation itself. We have used only local anesthesia for thirty-five years in many thousands of thyroidectomies. We have never done a tracheotomy in a goiter patient except in patients with carcinoma of the thyroid. We have had only five primary haemorrhages, with one death. We have never had a patient with bilateral recurrent laryngeal nerve injury. We have not lost a patient with exophthalmic goiter in eight years, and our mortality in toxic adenomatous goiters averages .07 per cent. The use of local anesthesia has materially contributed to these results. I would like to urge all young surgeons to employ it in their thyroidectomies. There is probably no major surgical procedure that can be so easily and satisfactorily handled by local anesthesia as thyroidectomy. I believe inhalation anesthesia should be avoided and intratracheal anesthesia should be reserved for removal of truly intrathoracic goiters, although in our cases to date we have not found it necessary.

Recurrent laryngeal nerve injury: Brien King made a great contribution to surgery of the thyroid in the phenomenal procedure he developed for the

relief of those most unfortunate patients with bilateral recurrent laryngeal nerve injury. In all large centers, at least one surgeon should perfect that procedure, and be prepared to deal with these patients.

COMMENT

Further intensive investigation should be carried out to determine more accurately the etiology of exophthalmic goiter, to develop means of offsetting the development of adenomatous goiters, to discover the toxic principle which I feel sure exists in a degenerating adenoma and in arousing the medical profession and the laity to the importance of early recognition of diseases of the thyroid gland. No responsible surgeon or physician would leave a mass in the breast till carcinoma develops—then why should an adenomatous goiter be left until cancer develops in it? While the incidence of carcinoma is relatively small, to the unfortunate victim of carcinoma it is 100 per cent. I have seen three patients with carcinoma of the thyroid in one day and five in one week, and three of these presented themselves too late for hope of a cure. No longer should any patient be advised "not to bother about the enlargement of the gland till the gland bothers him."

One needs only to observe the long drawn-out respiratory distress and suffering of a close personal friend with inoperable carcinoma of the thyroid, to have forever impressed on his mind the necessity for the most thorough examination of the thyroid gland of every patient who presents himself for examination, having constantly in mind that digital palpation of the thyroid gives us more direct information than any other diagnostic measure or combination of measures. This essential fact and simple, sensible diagnostic procedure is too often entirely forgotten in routine physical examination or only perfunctorily carried out, and in itself largely accounts for the extremely toxic patients we still have to deal with, and the relatively high percentage of carcinomas of the thyroid seen by those of us dealing with large numbers of goiters. Every member of this Association knows that this unfortunate situation is due to lack of appreciation on the part of the physician of the necessity for determining the presence or absence of a palpable gland, and to lack of knowledge on the part of the laity that if they have a goiter they should at once seek experienced professional advice in regard to it. The members of this Association must accept responsibility in their own neighborhood in arousing the medical profession and the laity to the danger of neglecting thyroid disease.

SUMMARY

The importance of early recognition and treatment of diseases of the thyroid gland is stressed. The relative values of treatment with goitrogenic drugs, radioactive iodine, and surgery are discussed.

EXPERIENCES WITH THYROIDECTOMY IN A THYROID CLINIC*

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THE following is an account of the experiences and the results of handling patients by the Thyroid Clinic of the University of California Hospital. The Clinic is operated by a committee comprised of members from the Divisions of Medicine, Surgery, Pathology and Radiology. The majority of clinic patients are cared for by this group. The interest in thyroid disease in this institution was inaugurated in 1903 by Dr. Wallace I. Terry, who became Professor of Surgery in 1912, and Professor Emeritus in 1929. Because of his exceptional ability as a teacher, observer and surgeon and his success in the management of these patients, a thyroid center was developed at this hospital where contributions were made regarding technic of thyroidectomy, method of recognition of the parathyroid glands by gross appearance and a method for their preservation, subtotal thyroidectomy rather than stage procedures in all cases, exophthalmos and an operative procedure for the correction of progressive exophthalmos, tumors of the thyroid gland, hyperventilation syndrome, pioneer work in the use of radioactive iodine therapeutically for Graves' disease, and many other thyroid problems.

From July, 1935, to January, 1948, the Thyroid Clinic was under the directorship of Dr. Mayo H. Soley, who was responsible for the medical appraisal and follow-up of the 1042 clinic patients who attended the Thyroid Clinic and were operated upon for thyroid disease. The results following surgical therapy are tabulated by the group under his supervision rather than by the operating surgeon. From 80 to 90 per cent of the operations were performed by resident staff members late in their training period, with or without operative supervision by a senior surgeon.

Of the 1042 patients operated upon for thyroid disease during this 12½-year period, about one half had hyperthyroidism (Table 1). The incidence of hypothyroidism postoperatively was 16.6 per cent (Table 2); myxedema 6.6 per cent; recurrences 2.8 per cent; hypoparathyroidism, 0.85 per cent; vocal cord paresis 3.2 per cent and paralysis 2.5 per cent, total 5.7 per cent. Limitation of motion or weakness of one vocal cord, indicating that the laryngeal nerve fibers were intact, was termed paresis; if, however, there

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was a complete abductor paralysis, the cord was said to be paralyzed. These examinations were conducted by members of the Department of Otolaryngology. Postoperative fever of over 38.5° C. occurred in 4.9 per cent of patients; thyroid crisis in 0.9 per cent. The over-all operative mortality rate was 0.6 per cent.

TABLE 1. CLASSIFICATION OF CASES

	Number	Per cent
Toxic diffuse goiter	379	36.4
Toxic nodular goiter	179	17.2
Nontoxic nodular goiter	389	37.3
Chronic thyroiditis	47	4.5
Carcinoma	48	4.6
Total	1042	100.0

TABLE 2. THYROID CLINIC, 1042 OPERATIONS, JULY, 1935–JANUARY, 1946

	Incidence per cent
Hypothyroidism	16.6
Myxedema	6.6
Recurrence	2.8
Hypoparathyroidism	0.8
Vocal cord paresis	3.2
Vocal cord paralysis	2.5
Fever (over 38.5° C.)	4.9
Crisis	0.9
Mortality	0.6

HYPERTHYROIDISM

During this period no pole ligations or lobectomies were performed for toxic goiter; all operations were of the subtotal thyroidectomy type. This group felt that with adequate preparation for surgery these patients would do better postoperatively if the complete operation were performed, since any remaining tissue would secrete increased amounts of thyroid hormone. In the years before the use of thiouracil, the majority of patients were prepared at home and allowed to rest in the hospital for three or four days under the administration of Lugol's solution, and then operated upon. The patient with severe hyperthyroidism required preoperative hospitalization for a period averaging seventeen days and postoperative hospitalization for five or six days (Table 3). Experiences with the use of propylthiouracil

during the past two years have led to the preparation of the patient with severe hyperthyroidism as an ambulatory patient. He is often able to con-

TABLE 3. SEVERE HYPERTHYROIDISM
Hospitalization

	Hospital Days	
	Preoperative	Postoperative
Lugol's solution	17	5–6
Propylthiouracil	1–2	5
Lugol's solution (now)		0–5

tinue his occupation, reporting at weekly intervals for a leucocyte and differential blood count, as well as a basal metabolic rate when indicated. Patients now require only one to two days preoperative hospital care and five days postoperative care under this regimen. When Lugol's solution has been used, it has usually been discontinued at the time of surgery, although some patients received the drug during their five-day postoperative stay. We have thought that the use of iodine postoperatively after an adequate subtotal thyroidectomy is without immediate benefit, and if continued, may encourage the development of hypothyroidism.

Toxic diffuse goiter

During this period 379 patients have been operated upon for toxic diffuse goiter (Table 4). At this Clinic the operation is almost always conducted under general anesthesia consisting of nitrous oxide and oxygen with or without sodium pentothal intravenously. As a direct result of Doctor Terry's practices the ribbon muscles are not transected except in the presence of an unusually large goiter or difficult operative procedure. Anatomi-

TABLE 4. TOXIC DIFFUSE GOITER
379 Operations

	Incidence per cent
Hypothyroidism	20.5
Myxedema	9.2
Recurrence	3.6
Hypoparathyroidism	1.5
Vocal cord paresis	3.3
Vocal cord paralysis	2.7
Fever (over 38.5° C.)	6.6
Crisis	1.5
Mortality	1.0

cal thyroidectomy is performed by an intracapsular excision with preservation of lateral and posterior capsule, without visualization of the recurrent laryngeal nerves. Generally between 3 and 4 grams of thyroid tissue is left behind. The weight of the remaining tissue can be accurately estimated by weighing an equal-size piece of the tissue removed and observing the amount left behind.

Hypothyroidism developed in 20.5 per cent of the patients with this type of goiter and required thyroid administration; myxedema occurred in 9.2 per cent. Both groups were controlled by administration of thyroid substance. There were recurrences in 3.6 per cent which were controlled by reoperation or x-ray therapy. Hypoparathyroidism occurred in 1.5 per cent; vocal cord paresis in 3.3 per cent and paralysis in 2.7 per cent, total 6 per cent; fever in 6.6 per cent; and thyroid crisis in 1.5 per cent. The mortality rate of this series was 1 per cent.

Toxic nodular goiter

Table 5 shows the follow-up results of 179 patients operated upon for toxic nodular goiter. The incidence of hypothyroidism was 21.2 per cent and myxedema 5.5 per cent. It has been our practice to be more radical in the excision of the surrounding thyroid proper in patients with toxic nodu-

TABLE 5. TOXIC NODULAR GOITER
179 Operations

	Incidence per cent
Hypothyroidism	21.2
Myxedema	5.5
Recurrence	0.5
Hypoparathyroidism	0.5
Vocal cord paresis	4.0
Vocal cord paralysis	3.1
Fever (over 38.5° C.)	7.7
Crisis	2.2
Mortality	0.5

lar goiter, particularly if there is evidence of hyperplasia as well. In this group 0.5 per cent of patients had recurrences, and 0.5 per cent developed hypoparathyroidism. Vocal cord paresis occurred in 4.0 per cent and paralysis in 3.1 per cent, total 7.1 per cent. Twelve of these patients had had previous thyroidectomy at some other institution. Febrile reaction was present in 7.7 per cent; thyroid crisis in 2.2 per cent. The mortality rate in this group was 0.5 per cent.

Ninety-five per cent of both toxic groups achieved what could be called good results.

NONTOXIC NODULAR GOITER

Patients with nontoxic nodular goiter made up the largest group operated upon during this period (Table 6). The incidence of hypothyroidism was 10.5 per cent and myxedema 4.3 per cent. This low percentage compared to that in the toxic group was achieved by preserving all paranodular tissue in order to reduce the incidence of hypothyroidism. There was a recurrence rate of 1.7 per cent in this group; hypoparathyroidism took place in 0.5 per cent; and vocal cord paresis in 2.3 per cent or paralysis in 2.3 per cent, total 4.6 per cent; fever occurred in 3 per cent. The mortality rate was 0.5 per cent.

TABLE 6. NONTOXIC NODULAR GOITER

389 Operations

	Incidence per cent
Hypothyroidism	10.5
Myxedema	4.3
Recurrence	1.7
Hypoparathyroidism	0.5
Vocal cord paresis	2.3
Vocal cord paralysis	2.3
Fever (over 38.5° C.)	3.0
Crisis	0.0
Mortality	0.5

CHRONIC THYROIDITIS

There were 47 patients with chronic thyroiditis (Table 7) with a high incidence of hypofunction postoperatively, 25.5 per cent developing hypothyroidism and 12.7 per cent myxedema. This was to be expected because of the partial ablation of functioning thyroid tissue by either the Hashimoto or Reidel type of chronic thyroiditis. There was a high incidence (12.7 per cent) of recurrence in this group. It was the practice until five years ago, in patients with thyroiditis, merely to split the isthmus and take a biopsy because of the likelihood of ensuing hypothyroidism. More recently, however, subtotal thyroidectomies have been performed for chronic thyroiditis without recurrences. These patients are usually then given thyroid substance. Vocal cord paresis was present in 4.8 per cent and paralysis in 3.8 per cent, total, 8.6 per cent. This high incidence is due to the adherence of the gland to the surrounding structures as well as to infiltra-

TABLE 7. CHRONIC THYROIDITIS
47 Operations

	Incidence per cent
Hypothyroidism	25.5
Myxedema	12.7
Recurrence	12.7
Hypoparathyroidism	0.0
Vocal cord paresis	4.8
Vocal cord paralysis	3.8
Fever (over 38.5° C.)	1.5
Crisis	0.0
Mortality	0.0

tion by the fibrous type of thyroiditis which may have been present preoperatively or have taken place postoperatively. Only 1.5 per cent showed febrile rise, and there were no deaths.

SINGLE NODULES

In a paper presented before this Association last year the high incidence of malignant tumor found in patients with a solitary nodule was reported from this Clinic. In 15.6 per cent of such patients malignant tumors were encountered (Table 8), whereas the incidence in patients with multiple nodules is 4.2 per cent. Because of the large percentage of unclassified tumors, when the intracystic papillomas and simple adenomas are added to the malignant group, it is seen that half of the patients with solitary

TABLE 8. PATHOLOGIC CLASSIFICATION OF 96 SOLITARY NODULES

	Number	Per cent	
Involutionary nodule	38	39.5	
Cyst	2	2.1	
Thyroiditis	1	1.0	
Unclassified	18	18.7	
Intracystic papilloma	1	1.0	
Adenoma	21	21.8	
Adenoma with invasion	2	2.1	15.6
Malignant adenoma	2	2.1	
Carcinoma	11	11.4	

nodules may have either benign or malignant neoplasms. On the basis of this percentage it has been our practice, when operating on patients with a solitary thyroid nodule, to do a lobectomy on the affected side, or remove

the isthmus with a good margin on either side, should the nodule arise at that point. If after its removal the nodule shows any evidence of malignancy, the remaining thyroid tissue should be removed. Because of the risk of infiltration of malignancy in this group, we consider that lobectomy is preferable to local excision. If after removal of the lobe there is gross or microscopic evidence of malignancy, the other lobe is removed. In many instances we feel that it is difficult or impossible for the surgeon to differentiate involutionary nodules, simple adenoma and malignant tumor in the thyroid gland, regardless of consistency, until after the specimen is excised.

CARCINOMA OF THE THYROID

During this period 48 patients were operated upon for carcinoma of the thyroid (Table 9). It has been our practice to do a complete thyroidectomy on patients with carcinoma of the thyroid, and if there is lymph node involvement, which when present is usually on the same side as the involved lobe, to do a deep neck dissection which consists of removal of the sterno-

TABLE 9. CARCINOMA OF THYROID
48 Operations

	Incidence per cent
Hypothyroidism	8.3
Myxedema	2.0
Recurrence (local)	6.2
Hypoparathyroidism	2.0
Vocal cord paresis	10.7
Vocal cord paralysis	8.0
Fever (over 38.5° C.)	2.0
Crisis	0.0
Mortality	2.0

cleidomastoid muscle, omohyoid and ribbon muscles, internal jugular vein, and the lymph node chains in this region. Our experiences have led us to believe that aberrant thyroids are in reality lymph node metastases from carcinoma of the thyroid. In all the patients that we have seen with aberrant thyroid tissue we have been able to demonstrate carcinoma in the thyroid gland even though only in microscopic amounts. It has been our practice to do a complete neck dissection on the affected side and a complete thyroidectomy in such patients. Table 9 shows a low incidence of hypofunction. There were 8.3 per cent of patients with hypothyroidism and 2.0 per cent with myxedema. In 6.2 per cent of patients there was a local recurrence of the carcinoma. Two per cent showed hypoparathyroid-

ism and there were 18.7 per cent with vocal cord paresis or paralysis. The high incidence of vocal cord paralysis in this group is explainable by invasion of the nerve by carcinoma tissue as well as by the difficulties encountered in operations on these infiltrating fixed tumor masses. Mortality rate in this group was 2 per cent.

In patients with carcinoma of the thyroid, careful palpation of the neck for lymph node metastases should be done, as well as roentgenologic examination to rule out more remote metastases. In the patients with aberrant thyroid tumors some lymph node structure is encountered at the periphery of the nodule; but in those in which the lymph node is completely replaced, we have always been able to find carcinoma in the thyroid gland.

SUMMARY

In the Thyroid Clinic of the University of California Hospital, during a 10½-year period, 1042 patients were operated on for thyroid disease. Data are presented giving the incidence of complications and sequelae in relation to the types of goiter removed at operation.

ACKNOWLEDGMENT

Acknowledgment is made to Miss Jean Hitch for the compilation of these data.

Announcement of the 1949 Meeting of the Association for the Study of Internal Secretions

The 31st Annual Meeting of the Association for the Study of Internal Secretions will be held at Haddon Hall, Atlantic City, New Jersey, June 3 and 4, 1949.

Inasmuch as the American Medical Association will be meeting in Atlantic City the following week, it is extremely important that hotel reservations be made at once directly with the hotel.

Further details concerning the meeting will be published at a later date.

Announcement of the Awards of the Association for 1949

Nominations for Awards

Three Awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each Award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma. All nominations, accompanied by a statement of the importance of the nominee's contributions to endocrinology and a bibliography of his most important papers with reprints if possible, should be sent to Dr. Turner's office not later than March 15, 1949.

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E.

Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. Edward A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori and in 1948 to Dr. Fuller Albright. No award was made in 1943. No age or special limitation is stipulated by the donor of the Award.

THE CIBA AWARD

The Ciba Award, established in 1942, is given in recognition of the meritorious accomplishment of an investigator, not over 35 years of age, in the field of clinical or preclinical endocrinology. In 1944 the Award was given to Dr. E. B. Astwood; in 1945 to Dr. Jane Anne Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li and in 1948 to Dr. Carl G. Heller. The Award is for $1,200.00. If within two years of the date of the Award, the recipient chooses to use it to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

THE AYERST, McKENNA & HARRISON FELLOWSHIP

The first Ayerst, McKenna & Harrison Fellowship was given to Dr. Samuel Dvoskin in 1947 and in 1948 it was given to Dr. Ernest M. Brown, Jr. This Fellowship is designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. The Fellowship may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend for the Fellowship will vary in accordance with the qualifications of the appointee, but will not exceed $2500.00. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. The nominee must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals, submit a program of proposed study, indicate one or more institutions where the proposed program shall be carried out and submit statements of approval from the investigators with whom he proposes to conduct his research.

ANNOUNCEMENT OF THE VAN METER PRIZE AWARD OF THE AMERICAN GOITER ASSOCIATION

The American Goiter Association again offers the Van Meter Prize Award of three hundred dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Asso-

ciation which will be held in Madison, Wisconsin, May 26, 27 and 28, 1949, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length, and must be presented in English. A typewritten double spaced copy should be sent to the Corresponding Secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia not later than March 15, 1949. The Committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association. This will not prevent its further publication, however, in any journal selected by the author.

Announcement of Post-Graduate Course In Endocrinology

THE AMERICAN COLLEGE OF PHYSICIANS

November 1–6, 1948

University of Illinois
College of Medicine

LaSalle Hotel
LaSalle and West Madison Street
Chicago, Illinois
Franklin 0700

WILLARD O. THOMPSON, M.D., F.A.C.P., *Director*

(Minimal Registration, 50; Maximal Registration, 100)

Fees: A.C.P. Members, $30.00; Non-Members, $60.00

This course represents an intensive review of recent developments in the field of endocrinology by leading teachers from all over the United States and Canada. It offers an opportunity for physicians to bring themselves up to date in this rapidly developing field of medicine. The following institutions are represented in the faculty:

The American College of Physicians
The American College of Surgeons
The American Medical Association
Association for the Study of Internal Secretions
The Chicago Medical Society
Cleveland Clinic
Columbia University College of Physicians and Surgeons
Cornell University Medical College
Duke University School of Medicine
Endocrinology
Harvard Medical School
Illinois State Medical Society
Johns Hopkins University
Journal of Clinical Endocrinology
Mayo Foundation, University of Minnesota
McGill University
Northwestern University Medical School
State University of Iowa College of Medicine
Tufts College Medical School
University of Chicago, The School of Medicine
University of Illinois College of Medicine
University of Oklahoma School of Medicine
University of Oregon Medical School
University of Southern California
University of Toronto Faculty of Medicine
Washington University School of Medicine

The physical arrangements for the course are excellent. The meetings will be held in the same hotel in which the men taking the course are living.

RESERVATIONS FOR HOTEL ROOMS: An adequate number of guest rooms have been set aside, and reservations should be made directly with Mr. Allan Stubbins, Resident Manager, LaSalle Hotel, Chicago, Illinois.

MEETING PLACE: LaSalle Hotel, LaSalle and West Madison Street. The LaSalle Hotel has recently been completely remodeled. It is one of the better hotels in Chicago and has the advantage of being in the loop. All sessions will be held in the Century Room on the nineteenth floor, where excellent facilities have been provided for the course.

LUNCHEON: A round table discussion will be held at luncheon from Monday, November 1 through Friday, November 5. On the first three days, i.e., Monday through Wednesday, the luncheon will be scheduled in the Grand Ballroom on the nineteenth floor. On Thursday, November 4 and Friday, November 5, the luncheons have been scheduled in the Lincoln Room and Press Gallery on the eighteenth floor. The hotel has made a special concession to us and has arranged for luncheon at $2.50 per person, which includes taxes and gratuities.

REFRESHMENTS DURING INTERMISSIONS: Light refreshments will be provided at a nominal charge during the morning and afternoon intermissions. These will be served in the Century Room on the ninteenth floor where the sessions will be held.

Officers of Instruction

Frank E. Adair, M.D., Associate Professor of Surgery, Cornell University College of Medicine

Willard M. Allen, M.D., Professor and Head of the Department of Obstetrics and Gynecology, Washington University School of Medicine.

J. S. L. Browne, M.D., Professor of Medicine, McGill University; Director, University Clinic, Royal Victoria Hospital.

C. L. Buxton, M.D., Associate Professor of Clinical Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons.

Warren H. Cole, M.D., Professor and Head of the Department of Surgery, University of Illinois College of Medicine.

Arthur R. Colwell, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School.

M. Edward Davis, M.D., The Joseph Bolivar DeLee Professor of Obstetrics and Gynecology, University of Chicago, The School of Medicine.

Edward W. Dempsey, M.D., Associate Professor of Anatomy, Harvard Medical School; Managing Editor, Endocrinology.

Earl T. Engle, M.D., Professor of Anatomy, Columbia University College of Physicians and Surgeons.

Frederick H. Falls, M.D., F.A.C.S., Professor and Head of the Department of Obstetrics and Gynecology, University of Illinois College of Medicine.

Ray Farquharson, M.D., Professor and Head of the Department of Medicine, University of Toronto Faculty of Medicine.

Edwin C. Hamblen, M.D., F.A.C.S., Professor of Endocrinology and Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine and Duke Hospital.

Norris J. Heckel, M.D., Clinical Professor of Urology (Rush), Department of Surgery, University of Illinois College of Medicine.

Carl G. Heller, M.D., Associate Professor of Medicine, University of Oregon Medical School.

Charles B. Huggins, M.D., Professor of Urology, University of Chicago, The School of Medicine.

Andrew C. Ivy, M.D., Distinguished Professor of Physiology and Vice-President, University of Illinois College of Medicine.

Harold L. Mason, M.D., Professor Physiological Chemistry, Mayo Foundation, University of Minnesota.

E. Perry McCullagh, M.D., Head of the Section of Endocrinology and Metabolism, Cleveland Clinic

Carl R. Moore, Ph.D., Professor and Head of the Department of Zoology, University of Chicago.

Warren O. Nelson, M.D., Professor of Anatomy, The State University of Iowa, College of Medicine; Chairman, Publications Committee, Association for the Study of Internal Secretions.

Gregory Pincus, M.D., Director of Laboratories, Worcester Foundation for Experimental Biology and Research Professor of Physiology, Tufts College Medical School.

Edward H. Rynearson, M.D., F.A.C.P., Consultant, Division of Medicine, Mayo Clinic; Associate Professor of Medicine, Mayo Foundation, University of Minnesota.

E. Kost Shelton, M.D., Sc.D., F.A.C.P., Associate Professor of Medicine, University of Southern California.

Danely P. Slaughter, M.D., Assistant Professor of Surgery and Director of Tumor Clinic, University of Illinois College of Medicine.

Samuel Soskin, M.D., Ph.D., Professorial Lecturer in Physiology, University of Chicago; Medical Director, Michael Reese Hospital; Director, Medical Research Institute, Michael Reese Hospital; Dean Michael Reese Hospital Postgraduate School.

Paul M. Starr, M.D., Clinical Professor of Medicine, University of Southern California.

Willard O. Thompson, M.D., F.A.C.P., Clinical Professor of Medicine, University of Illinois College of Medicine; Managing Editor, Journal of Clinical Endocrinology.

Henry H. Turner, M.D., Associate Professor of Medicine and Associate Dean, University of Oklahoma School of Medicine; Secretary-Treasurer, Association for the Study of Internal Secretions.

Lawson Wilkins, M.D., Associate Professor Professor of Pediatrics, Chief of the Endocrine Division of Pediatrics, The Johns Hopkins Hospital.

Presiding Officers

Frank E. Adair, M.D., see Officers of Instruction.

Lowell T. Coggeshall, M.D., Professor and Chairman of the Department of Medicine, Dean of Division of Biological Science, University of Chicago, The School of Medicine.

Lester R. Dragstedt, M.D., F.A.C.S., Professor and Chairman of the Department of Surgery, University of Chicago, The School of Medicine.

Warren W. Furey, M.D., Past President, The Chicago Medical Society.

Edwin S. Hamilton, M.D., Trustee, The American Medical Association.

Julius H. Hess, M.D., Professor Emeritus of Pediatrics, University of Illinois College of Medicine.

Ford K. Hick, M.D., Associate Professor of Medicine, University of Illinois College of Medicine.

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Grant H. Laing, M.D., Assistant Professor of Medicine, Northwestern University Medical School.

Malcolm T. MacEachern, M.D., Associate Director, The American College of Surgeons.

J. Roscoe Miller, M.D., Associate Professor of Medicine and Dean of Northwestern University Medical School

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James P. Simonds, M.D., Professor Emeritus of Pathology, Northwestern University Medical School.

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Albert Vanderkloot, M.D., Associate Clinical Professor of Medicine, University of Illinois College of Medicine.

George E. Wakerlin, M.D., Professor of Physiology and Head of the Department, University of Illinois College of Medicine.

John B. Youmans, M.D., Dean of University of Illinois College of Medicine.

Outline of Course

MONDAY, NOVEMBER 1, 1948

WILLARD O. THOMPSON, M.D., *Presiding*

A.M. Session—Century Room, 19th Floor, LaSalle Hotel

8:00– 9:00—Registration
9:00– 9:30—Dr. McCullagh: The Present Status of Non-Surgical Treatment of Hyperthyroidism.
9:30–10:00—Dr. Wilkins: Hypothyroidism in Childhood.
10:00–10:30—Dr. Moore: The Relation of Sex Hormones to Sexual Differentiation and Sex Abnormalities.
10:30–10:45—Intermission—Refreshments, Century Room, 19th Floor

CARL R. MOORE, PH.D., *Presiding*

10:45–11:15—Dr. Rynearson: Obesity.
11:15–11:45—Dr. Cole: The Present Status of the Treatment of Toxic Goitre.
11:45–12:15—Dr. Ivy: Gastro-Intestinal Hormones.
12:15–12:45—Dr. Wilkins: Sexual Infantilism and Sexual Precocity.
12:45– 2:00—Luncheon—Grand Ballroom, 19th Floor.

ROUND TABLE DISCUSSION

J. ROSCOE MILLER, M.D., *Presiding*

P.M. Session—Century Room, 19th Floor, LaSalle Hotel

2:00– 2:30—Dr. Wilkins: Genetic and Endocrine Factors Affecting Somatic Growth and Development
2:30– 3:00—Dr. Davis: Basal Body Temperature in the Study of Ovarian Activity.
3:00– 3:30—Dr. McCullagh: Is There A Male Climacteric?
3:30– 4:00—Dr. Soskin: The Pathologic Physiology of Diabetes.
4:00– 4:15—Intermission—Refreshments, Century Room, 19th Floor.

ALBERT VANDERKLOOT, M.D., *Presiding*

4:15– 4:45—Dr. Rynearson: Overfunction of the Adrenal Cortex.
4:45– 5:15—Dr. Moore: Reactions of the Ovary after Chemical Injury of Cortex.
5:15– 5:45—Dr. Thompson: Hypopituitarism.

TUESDAY, NOVEMBER 2, 1948

LOWELL T. COGGESHALL, M. D., *Presiding*

A.M. Session—Century Room, 19th Floor, LaSalle Hotel

9:00– 9:30—Dr. Rynearson: Disturbances of the Pituitary Gland.
9:30–10:00—Dr. Wilkins: Heterosexual Development: Genetic vs. Endocrine Types.
10:00–10:30—Dr. McCullagh: The Office Management of the New Diabetic Patient.
10:30–10:45—Intermission—Refreshments, Century Room, 19th Floor

PAUL S. RHOADS, M.D., *Presiding*

10:45–11:15—Dr. Farquharson: Clinical and Pathological Manifestations of Simmonds' Disease.
11:15–11:45—Dr. Mason: The Urinary Corticosteroids.
11:45–12:15—Dr. Shelton: Growth and Development.

12:15–12:45—Dr. Colwell: Comparison of Intermediate Insulins.
12:45– 2:00—Luncheon—Grand Ballroom, 19th Floor

ROUND TABLE DISCUSSION

JOHN B. YOUMANS, M.D., *Presiding*

P.M. Session—Century Room, 19th Floor, LaSalle Hotel

2:00– 2:30—Dr. Farquharson: Effect of Prolonged Administration of Thyroid on B.M.R. of People with an Intact Thyroid Gland.
2:30– 3:00—Dr. Shelton: Somatic Insults and Pseudo-Endocrinopathies.
3:00– 3:30—Dr. Farquharson: Anorexia Nervosa.
3:30– 4:00—Dr. Turner: Dwarfism.
4:00– 4:15—Intermission—Refreshments, Century Room, 19th Floor

LESTER R. DRAGSTEDT, M.D., *Presiding*

4:15– 4:45—Dr. Thompson: Various Types of Dwarfism and Their Treatment.
4:45– 5:15—Dr. Starr: The Heart in Thyroid Disease.
5:15– 5:45—Dr. Slaughter: The Hormonal Treatment of Inoperable Carcinoma of the Breast.

WEDNESDAY, NOVEMBER 3, 1948

LEROY H. SLOAN, M.D., *Presiding*

A.M. Session—Century Room, 19th Floor, LaSalle Hotel

9:00– 9:30—Dr. Allen: Simple Methods of Help in the Diagnosis of Adrenal Tumor.
9:30–10:00—Dr. Mason: Significance of Urinary Steroids in Differentiation Between Adrenal Cortical Hyperplasia and Adrenal Cortical Tumors.
10:00–10:30—Dr. Turner: Syndromes of Hyperadrenalism.
10:30–10:45—Intermission—Refreshments, Century Room, 19th Floor

HENRY H. TURNER, M.D., *Presiding*

10:45–11:15—Dr. Allen: Male and Female Pseudohermaphrodism and Adrenal Tumors.
11:15–11:45—Dr. Starr: The Diagnosis of Atypical Cases of Hyperthyroidism.
11:45–12:15—Dr. Browne: Endocrine Physiopathology of Menstruation and Pregnancy.
12:15–12:45—Dr. Allen: Functional Uterine Bleeding.
12:45– 2:00—Luncheon—Grand Ballroom, 19th Floor

ROUND TABLE DISCUSSION

FORD K. HICK, M.D., *Presiding*

P.M. Session—Century, 19th Floor, LaSalle Hotel

2:00– 2:30—Dr. Engle: Physiology of Menstruation.
2:30– 3:00—Dr. Mason: 17-Ketosteroids and Their Significance in Disease.
3:00– 3:30—Dr. Allen: Hormonal Changes During Pregnancy.
3:30– 4:00—Dr. Mason: Physiologic Effects of Adrenal Cortical Hormones.
4:00– 4:15—Intermission—Refreshments, Century Room, 19th Floor

GEORGE E. WAKERLIN, M.D., *Presiding*

4:15– 4:45—Dr. Thompson: Androgen Therapy.
4:45– 5:15—Dr. Shelton: Use of Testosterone in Prematurity.
5:15– 5:45—Dr. Starr: Experience with Anti-Thyroid Drugs in the Treatment of Hyperthyroidism.

THURSDAY, NOVEMBER 4, 1948

EDWIN S. HAMILTON, M.D., *Presiding*

A.M. Session—Century Room, 19th Floor, LaSalle Hotel

9:00– 9:30—Dr. Hamblen: Apubescence and Hypopubescence of the Male.
9:30–10:00—Dr. Browne: Laboratory Aids in Endocrine Diagnosis.
10:00–10:30—Dr. Dempsey: Histophysiologic Considerations of the Endocrine System. (continued)
10:30–10:45—Intermission—Refreshments, Century Room, 19th Floor

EDWIN S. HAMILTON, M.D., *Presiding*

10:45–11:15—Dr. Thompson: Addison's Disease.
11:15–11:45—Dr. Dempsey: Histophysiologic Considerations of the Endocrine System. (continued)
11:45–12:15—Dr. Buxton: Investigation and Treatment of Amenorrhea.
12:15–12:45—Dr. Dempsey: Histophysiologic Considerations of the Endocrine System.
12:45– 2:00—Luncheon—Lincoln Room and Press Gallery, 18th Floor

ROUND TABLE DISCUSSION

WARREN W. FUREY, M.D., *Presiding*

P.M. Session—Century Room, 19th Floor, LaSalle Hotel

2:00– 2:30—Dr. Hamblen: Apubescence and Hypopubescence of the Female.
2:30– 3:00—Dr. Turner: Infantilism Associated with Ovarian Agenesis and Other Congenital Anomalies.
3:00– 3:30—Dr. Hamblen: Endocrinology and Clinical Conduct of the Female Climateric.
3:30– 4:00—Dr. Browne: Cushing's Syndrome.
4:00– 4:15—Intermission—Refreshments, Century Room, 19th Floor

JULIUS H. HESS, M.D., *Presiding*

4:15– 4:45—Dr. Engle: Male Hypogonadism.
4:45– 5:15—Dr. Nelson: Testicular Tumors.
5:15– 5:45—Dr. Engle: Testis Biopsies.

Evening Session

On Thursday evening, November 4, a joint session will be held with the North Side Branch of the Chicago Medical Society at the Drake Hotel. The schedule is as follows:

5:30 P.M.—Cocktails
6:30 P.M.—Dinner
8:00 P.M.—Scientific Meeting

Various members of the teaching faculty in this course will take part in the program. Those wishing to attend may obtain tickets at the Registration Desk.

FRIDAY, NOVEMBER 5, 1948

PERCY E. HOPKINS, M.D., *Presiding*

A.M. Session—Century Room, 19th Floor, LaSalle Hotel

9:00– 9:30—Dr. Heller: Study of Male Sterility—Use of Testicular Biopsy and Urinary Gonadotrophin Assays as a Guide to Prognosis and Therapy.
9:30–10:00—Dr. Nelson: Testicular Biopsy.

10:00–10:30—Dr. Heller: Hypogonadotrophic Eunuchoidism—Differential Diagnosis and Therapy with Chorionic Gonadotrophin and FSH.
10:30–10:45—Intermission—Refreshments, Century Room, 19th Floor

GRANT H. LAING, M.D., *Presiding*

10:45–11:15—Dr. Buxton: Problem of Sterility—The Investigation of the Sterile Couple.
11:15–11:45—Dr. Falls: The Use of Lutein Hormone in the Treatment of Abortion in Man.
11:45–12:15—Dr. Pincus: Estrogen Metabolism.
12:15–12:45—Dr. Adair: The Physical and Chemical Changes Resulting from Testosterone Therapy of Breast Cancer.
12:45– 2:00—Luncheon—Lincoln Room and Press Gallery, 18th Floor

ROUND TABLE DISCUSSION

JAMES P. SIMONDS, M.D., *Presiding*

P.M. Session—Century Room, 19th Floor, LaSalle Hotel

2:00– 2:30—Dr. Heckel: The Relationship of Diseases of the Endocrine System to Fertility in the Male.
2:30– 3:00—Dr. Pincus: Adrenal Cortex Hormones and Their Metabolism.
3:00– 3:30—Dr. Ivy: The Problem of Intersexuality.
3:30– 4:00—Dr. Buxton: The Investigation and Treatment of Menometrorrhagia.
4:00– 4:15—Intermission—Refreshments, Century Room, 19th Floor

MALCOLM T. MACEACHERN, M.D., *Presiding*

4:15– 4:45—Dr. Huggins: Endocrine Treatment of Prostatic Cancer.
4:45– 5:15—Dr. Huggins: Hormone Production by Testicular Tumors.
5:15– 5:45—Dr. Adair: X-ray Changes Resulting from Testosterone Therapy of Breast Cancer.

SATURDAY, NOVEMBER 6, 1948

FRANK E. ADAIR, M.D., *Presiding*

A.M. Session—Century Room, 19th Floor, LaSalle Hotel

9:00– 9:30—Dr. Nelson: Endocrine Physiology of Puberty.
9:30–10:00—Dr. Falls: The Relationship of Pregnancy to the Endocrine System.
10:00–10:30—Dr. Pincus: Ovulation.
10:30–10:45—Intermission—Refreshments, Century Room, 19th Floor

WILLARD O. THOMPSON, M.D., *Presiding*

10:45–11:15—Dr. Heller: The Male Climateric—Differential Diagnosis and Treatment.
11:15–11:45—Dr. Nelson: Endocrine Control of Reproduction in the Male.
11:45–12:15—Dr. Heckel: The Endocrine Treatment of Cancer of the Prostate.
12:15–12:45—Dr. Adair: The Effect of Testosterone Therapy on Advanced Breast Cancer.

The American College of Physicians Announces Its Annual Session At New York City, March 28-April 1, 1949

The American College of Physicians will conduct its 30th Annual Session at New York, N. Y., March 28 through April 1, 1949. Dr. Franklin M. Hanger, Jr., of New York City is the Chairman for local arrangements and the program of Clinics and Panel Discussions. The President of the College, Dr. Walter W. Palmer, Director of The Public Health Research Institute of the City of New York, Inc., and Professor Emeritus, Columbia University College of Physicians and Surgeons, is in charge of the program of morning Lectures and afternoon General Sessions.

Secretaries of medical societies are especially asked to note these dates and, in arranging meeting dates of their societies, to avoid conflicts with the College Meeting, for obvious mutual benefits.

Research Fellowships—The American College of Physicians

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1949-June 30, 1950. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from $2,200 to $3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1948. Announcement of the awards will be made as promptly as is possible.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: ROY HERTZ. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS.

PITUITARY

BENNETT, L. L., AND LI, C. H.: The effects of the pituitary growth and adrenocorticotropic hormones on the urinary glucose and nitrogen of diabetic rats, *Am. J. Physiol.* **150:** 400–404, 1947.

The purpose of this article is to report the effects produced in diabetic rats by chemically and biologically pure growth and adrenocorticotropic hormones.

In the experiments male rats of the Long-Evans strain (weight: approximately 200 Gm.) were used, in which diabetes mellitus was produced by intraperitoneal injection (on two successive days) of alloxan monohydrate (Eastman) at a dose level of 200 mg. per kilogram of body weight. Animals with persistent, severe diabetes mellitus, exhibiting a daily glycosuria of more than 3.5 Gm. were selected for study. Each animal was maintained on a constant food intake and weighed before feeding. Urine was collected daily under toluene and analysed for glucose and total nitrogen by the Shaeffer-Somogyi method and the micro-Kjeldahl procedure. The data for total reducing substances are reported.

The growth hormone (3 mg.) was injected subcutaneously three times a day for five or six days, and insulin (in the form of protamine zinc insulin) was administered once daily subcutaneously. The same was done with adrenocorticotropic hormone (3 mg. per day).

In these experiments the following results were obtained: growth hormone produced nitrogen storage and adrenocorticotropic hormone produced nitrogen loss in rats with alloxan-induced diabetes, both with and without exogenous insulin. Growth hormone occasionally produced an increase and adrenocorticotropic hormone consistently produced a marked increase of the glycosuria of rats with alloxan-induced diabetes, both with and without exogenous insulin.

Thus growth hormone is not diabetes-enhancing with regard to it effects upon nitrogen excretion, but may be so with regard to glycosuria (when administered at the higher dose level); and adrenocorticotropic hormone is diabetes-enhancing and "anti-insulin" in its effects on both nitrogen and glucose excretion in the diabetic rat, in that it produces the characteristic effects of insulin deficiency. It is also to be noted that the effects of growth hormone on nitrogen excretion were demonstrated more consistently than were its effects on glycosuria whereas for adrenocroticotropic hormone, the reverse was true.—E.C.R.

HORNE, S. F., AND MORRIS, L. M.: Use of posterior pituitary extract "Pituitrin" to measure renal function, *Am. J. M. Sc.* **213**: 68, 1947.

Seeking a simple and dependable renal function test which would be adaptable to office practice and would allow rapid evaluation of the concentration power of the kidneys, the authors compared the pituitrin test with a fluid restriction test in a series of patients with and without impaired renal function and in a group of patients with congestive heart failure, both before and after compensation. In addition, the effect of the patient's state of hydration on both tests was studied.

A total of 67 patients (ages 12 to 96 years) were divided into 5 groups: 1) a group of 14 patients without hypertension or evidence of renal disease, 2) 11 patients with hypertension who showed no evidence of renal disease, 3) 27 patients with impaired kidney function, 4) 10 patients with congestive heart failure, 5) 5 patients without evidence of kidney disease in whom the effect of the state of hydration was studied.

Statistical analysis of the first 3 groups indicated that the fluid restriction and pituitrin tests give extremely close agreement of the concentrating power of the kidney in patients without renal disease, but that they differ significantly in patients with impaired kidney function. The authors further conelude that pituitrin can be used as a substitute for the fluid restriction test to measure renal function and that it is a valuable addition to the group of renal function tests. They enumerate several advantages of this test, e.g., no prolonged period of fluid restriction; reliable in the presence of edema; no special preparation of patient necessary; completion of the test in two hours. This makes it valuable in preoperative cases where there is no much time for delay or when fluid restriction is contraindicated. The authors warn that the pituitrin is potentially dangerous in patients with angina pectoris and is contraindicated in pregnancy, even in the first trimester, because of the danger of uterine contractions and fetal death.—E.C.R.

THYROID

MAN, E. B.; CULOTTA, C. S.; SIEGFRIED, D. A., AND STILSON, C.: Serum precipitable iodine in recognition of cretinism and in control of thyroid medication, *J. Pediat.* **31**: 154, 1947.

In view of the fact that probably irrevocable damage occurs in children by the time clinical symptoms of cretinism become complete, the authors feel that recognition of thyroid hypofunction before all symptoms develop would permit earlier thyroid medication. Therefore they examined their data in order to find out whether or not the measurement of serum precipitable iodine is useful in the diagnosis of cretinism and in the differential diagnosis between cretinism and mongolism. Serum precipitable iodine and cholesterols were compared as to their usefulness in the diagnosis of cretinism.

The authors studied 6 cretin children after treatment with desiccated thyroid. The authors conclude that measurement of serum precipitable iodine is more reliable than evaluation of serum cholesterol in the diagnosis of cretinism, and discuss the clinical response in relation to the level of serum precipitable iodine after administration of different doses of desiccated thyroid.—E.C.R.

WILLIAMS, L. P., AND JANNEY, F. R.: Thiouracil in childhood hyperthyroidism, *J. Pediat.* **30**: 371, 1947.

In view of the fact that, as generally agreed, the thyroid hormone is important in the normal development of the child, the authors recommend a thorough medical trial be-

fore surgery is considered in childhood hyperthyroidism. They report 6 cases in which they used thiouracil with success, but are unable to evaluate these cases as to permanency of cure, since the period of observation has been too brief. No notable reactions to administration of thiouracil were observed. In the case of adolescent patients, the authors feel that thiouracil might well cause the symptoms of hyperthyroidism to remain in remission until controlled by the establishment of the more stable period of adulthood. Though subtotal thyroidectomy may be ultimately required, they feel that an advantage had been gained by retaining thyroid action at the time of the individual's greatest need.—E.C.R.

ADRENALS

BERGMAN, B.: Sex precocity and the adrenogenital syndrome, *J. Pediat.* **31**: 142, 1947.

The author outlines present-day concepts of sex precocity and the adrenogenital syndrome, with case histories.

After brief definitions of the terms sex precocity, precocious puberty, adrenogenital syndrome, pseudohermaphroditism, and true hermaphroditism, a detailed discussion of these follows, supported by case reports. Finally a differential diagnosis table of sex precocity and the adrenogenital syndrome is presented in the hope that it may help to provide a rapid method of differentiation of these cases.—E.C.R.

HARTMANN, A. F.: Adenoma of the adrenal cortex. Case 1, presented before the Clinical Conference at the St. Louis Children's Hospital, May 23, 1947. *J. Pediat.* **31**: 93, 1947.

The case of an 18-month-old girl showing great somatic growth, masculinizing changes and precocious sexual development was discussed, taking into consideration all the known different types of sexual precocity and their causes. On the basis of a thorough physical examination, urine and blood tests, x-rays and 17-ketosteroids, the clinical diagnosis of adenoma of the adrenal cortex was made, which was then confirmed after laparotomy when a tumor of the left adrenal gland was removed and examined.—E.C.R.

SNYDER, C. H., AND VICK, E. H.: Hypertension in children caused by pheochromocytoma, *Am. J. Dis. Child.* **73**: 581, 1947.

The authors present a group of cases of hypertension (illustrated by the 3 cases reported in this paper) in which surgical intervention may effect the immediate cure of an otherwise progressive and fatal hypertension. These are the cases due to pheochromocytoma or paraganglioma—tumors of chromaffin tissue which secrete epinephrine. Such tumors usually arise from the adrenal medulla, but occasionally develop from nests of chromaffin tissue in other parts of the body. Histologically, these are nearly always benign, and yet they may secrete so much epinephrine into the blood stream as to produce death from hypertensive cardiovascular disease. The clinical picture exhibited by these patients has been called the adrenal-sympathetic syndrome and is characterized most classically by paroxysms of hypertension. A great many, however, show only a steady progressive elevation of blood pressure.

Case No. 1 is the fourth reported in literature in which the patient was below 13 years of age. With earlier diagnosis the prognosis would have been much more favorable. Perirenal air studies proved of value in localization of the tumor mass.

Case No. 2 is the fifth recorded case of pheochromocytoma with hypertension in the

pediatric age group and the second such case in which cure was effected by operation. It is the first case at any age that has presented 2 tumors, one being intramedullary and the other extramedullary. It indicates the importance of considering pheochromocytoma in the differential diagnosis of hypertension in children, even when the hypertension is continuous rather than paroxysmal. Again perirenal air studies revealed the tumor.

Case No. 3 is the sixth recorded case and probably presents an example of paroxysmal hypertension that went on to become continuous. Had the original attacks been recognized for hypertensive episodes, it is possible that the diagnosis could have been made at the time when the tumor was operable. Hence the importance of such procedures as the histamine test by which paroxysms of hypertension may be induced at will. Another important fact is that the diagnosis of pheochromocytoma can be made even without roentgenologic evidence of a tumor, in which case laparotomy will almost invariably reveal its location.

The authors present a review of the literature which shows that only 84 proved cases of hypertension due to pheochromocytoma are reported to date. Of these only 3 prior to this report have occurred in children. These 3 cases are described briefly. The clinical features, laboratory data, diagnosis and treatment of the disease are reviewed.—E.C.R.

GONADS

BREWER, J. I., AND JONES, H. O.: The time of ovulation, *Am. J. Obst. & Gynec.* **53**: 637–644 (April) 1947.

The authors studied the surgical specimens of ovary, ovaries or resected portions of ovaries and endometrium in 100 women who had menstrual cycles within the limits established for normal. Accurate menstrual histories were obtained. The patients were not selected in any way. Fifty-three of the patients were operated upon after the fifteenth day of the cycle.

The range of time of ovulation, as determined by subtracting the estimated age of the corpus luteum from the day of the cycle upon which the patient was operated on, varied from the eighth through the nineteenth days of the cycle. Of the 54 patients who ovulated, 36 ovulated on days 12, 13, 14, and 15; 5 ovulated on days 16, 17 and 19; and 13 ovulated on days 8, 9, 10 and 11.

Forty-six patients had not ovulated during the cycle under study. All of these except 4 were operated upon between the first and fourteenth days of the cycle. Seven were operated on day 13, and three on day 14. These and the 4 who had not ovulated by day 17 and 18, with one exception, showed mature follicles and undoubtedly would have ovulated. The one exception was the only patient in the entire group of 100 women in whom failure of ovulation was strongly indicated. Degenerating corpora lutea of the previous cycle were demonstrated in the ovaries of the 46 patients who had not as yet ovulated during the cycle studied.

The authors conclude that it is possible to estimate the age of corpora lutea accurately by histologic and cytologic methods that have been previously described in detail. —C.D.D.

BUNDE, C. A.: An evaluation of the pregnancy test based on ovarian hyperemia in the immature rat, *Am. J. Obst. & Gynec.* **53**: 317–320 (Feb.) 1947.

The ovarian hyperemia pregnancy test was employed in a series of women in whom pregnancy was suspected. Using two rats per test, an accuracy of 84.5 per cent was ob-

tained in 108 determinations. Using three rats per test, in 84 assays, a 90.5 per cent accuracy was secured.

Three methods of injection of urine were used: (a) 1.5 cubic centimeters intraperitoneally with autopsy 2 hours later, (b) subcutaneous administration of 2 cubic centimeters with autopsy 6 hours afterwards, and (c) initial subcutaneous dose of 2 cubic centimeters followed in 4 hours by 1.5 cubic centimeters intraperitoneally with autopsy 6 hours after the original injection. No significant difference could be found in the accuracy of these three methods of injection.—C.D.D.

DOUGLAS, M.: Masculinizing tumor of the ovary of the adrenal type, *Am. J. Obst. & Gynec.* **53:** 190–198 (Feb.) 1947.

A case report is presented of a 48-year-old woman in whom an adrenal cortical tumor of the right ovary was removed. The patient presented much of the usual picture of hyperactivity of the adrenal cortex, which included: tendency towards hypertension, polycythemia, normal carbohydrate metabolism, generalized hirsutism, hypertrophied clitoris, deepening of the voice, loss of much scalp hair. The excretion of urinary 17-ketosteroids was 11.6 milligrams per 24 hours and the androgen excretion as determined by bio-assay was 33 international units. The urinary gonadotropin level was less than 4 mouse uterine units per 24 hours. Also, preoperatively, no pregnandiol was found in the urine and the estrogen level was less than 75 international units in 24 hours. The 17-ketosteroid and androgen levels were within normal range for adult females.

Postoperatively, the urinary excretion of hormones per 24 hours was as follows: 17-ketosteroids, 3.4 to 8.5 milligrams; and gonadotropin 64 mouse uterine units.

A two year follow-up has shown complete restitution of normal feminine facies and habitus except that facial hair requires shaving every 3 to 4 days. The clitoris has returned to normal.—C.D.D.

EIDELSBERG, J.: Estrogens in urine and cytology of vaginal smears after the use of an estrogenic cream, *Am. J. M. Sc.* **214:** 630, 1947.

The author undertook these studies in order to observe the effect of estrogen, administered by inunction, on the estrogen content of urine, and on the histologic picture of vaginal smears.

The fluctuations in estrogen excretion in 4 untreated controls and in 14 patients, before and during the use of an estrogen cream by facial inunction were similar in pattern and not significantly different in amount. Likewise, their vaginal smears appeared to show no significant alteration in cytologic cycles. Therefore, in the amounts and by the method applied (3750 I.U. per week, or ±535 I.U. daily) the estrogen cream did not appear to produce any systemic effect.—E.C.R.

HARDING, F. E.: Effect of pregneninolone on the menstrual cycle of adolescent girls with oligomenorrhea or amenorrhea, *Am. J. Obst. & Gynec.* **53:** 279–284 (Feb.) 1947.

Forty-six adolescent girls ranging in age from 11 to 19 years, who had no or infrequent menstrual periods, were treated with pregneninolone or anhydrohydroxy-progesterone. Five had never menstruated, in 32 the menses were always infrequent and in 9, usually so. Most of the patients had functional complaints which were believed to be associated with the delay in menstruation.

The usual dosage was 5 milligrams of pregneninolone daily from the eighteenth day of the menstrual cycle until bleeding started. Patients who were not menstruating were either treated for 10 days each month or continuously until bleeding started.

Eighty-seven per cent of 33 patients with cycles of 3 months or less were improved. The results were poor in those with cycles of 6 months or longer, and none of the primary amenorrhea group menstruated in association with this therapy. Seventy-two per cent of the patients with dysmenorrhea were relieved during the time the therapy was given.

The effect of this therapy is largely temporary but a follow-up of 30 per cent of the patients with shortened cycles showed that 12 continued to bleed approximately on time during the six months following the completion of treatment.—C.D.D.

HIRST, J. C.: Conservative treatment and therapeutic test for endometriosis by androgens, *Am. J. Obst. & Gynec.* **53:** 483–487 (March) 1947.

Nineteen patients, with varying degrees of clinically diagnosed external endometriosis were treated usually with 150 to 225 milligrams of testosterone propionate in oil intramuscularly over a period of 2 to 3 weeks, followed by 10 milligrams of methyl testosterone orally for variable periods up to three or more years in 3 patients. Other than slight virilism and occasional acne, reactions have been negligible. The author finds the above regimen valuable as regards rapid reduction of pain, tenderness and swelling of grossly cystic ovarian endometriomas. Very brief reports of these 19 patients are presented.—C.D.D.

KARNAKY, K. J.: Estrogenic tolerance in pregnant women, *Am. J. Obst. & Gynec.* **53:** 312–316 (Feb.) 1947.

Daily doses of diethylstilbestrol up to 1000 milligrams were administered to pregnant women. Only those who received 500 milligrams or more daily became nauseated. The total dosages given throughout pregnancies varied from 790 to 24,050 milligrams. In no instance was abortion caused by the administration or the withdrawal of this substance.

All babies were found to be normal. They all exhibited a darkening of the areolae about the nipples, and of the labia and linea alba, similar to that of their mothers.—C.D.D.

LEATHEM, J. H. AND RAKOFF, A. E.: Are antihormones formed during pregnancy? *Am. J. Obst. & Gynec.* **51:** 97–99 (Jan.) 1946.

The sera from 10 patients, two to four weeks postpartum, were tested for the presence of antigonadotropic substances against chorionic gonadotropin and human pituitary. All tests were uniformly negative. Thus gonadotropins of homologous source are not antigenic and no evidence is available for an antihormonic cause of amenorrhea following parturition. (Author's Summary).—C.D.D.

MCKELVEY, J. L., AND SAMUELS, L. T.: Irregular shedding of the endometrium, *Am. J. Obst. & Gynec.* **53:** 627–636 (April) 1947.

The author presents a report on irregular shedding which is one of the abnormalities of true menstruation. It is characterized clinically by prolongation of flow and increase in amount of blood loss; histologically by retention over variable periods of time of ab-

normal amounts of secretory endometrium; and endocrinologically by excretion of sodium prenanediol during the time of the uterine bleeding.

The author reports data on 34 patients in whom the condition was found. It may occur at any time during the reproductive epoch but the majority of patients are in the 35 to 45-year age group. There is little effect on childbearing. However, in 9 patients the onset was immediately postpartum. The length of bleeding was 7 to 10 days in 15 patients; 11 to 14 days in 9 patients; and 15 days or more in 10 patients. All patients showed varying degrees of anemia. The duration of the cycle was as follows: in 17 patients, 25 to 35 days; in 8, less than 25 days; and in 9, too irregular to classify.

The associated gynecologic pathology was as follows: endometrial polyp, 1 patient; uterine myomas, 9 patients; proven history of previous endometrial hyperplasia, 2 patients.

The author recommends no special treatment. Repeated curettage as indicated is used in the patients under 40 years of age along with general measures. In the older patients the author uses x-ray sterilization as the treatment of choice if the simple measures fail.

Brief histories of 6 patients are presented.—C.D.D.

PROCTER, T. M., AND DICKINSON, K.: The office study of infertility, *Am. J. Obst. & Gynec.* **53**: 65–74 (Jan.) 1947.

The authors find that one out of every four couples who complain of infertility succeed in producing a normal viable offspring under treatment. They studied 210 women, 153 of whom had had no previous pregnancies. The male was studied only via postcoition and condom-bottle sperm tests. Abnormalities in the male, evaluated by these studies only, were found in 50 per cent of the husbands. The wives' studies included history, physical examination, determination of pH of vagina and cervix, postcoition test, tubal insufflation with air and occasionally a hysterosalpingogram, basal metabolic determination and endometrial biopsy.

Outstanding cervical pathology was found in 59 per cent of these women, and surgical correction was followed by pregnancy in 21 out of 50 patients. Thyroid extract was given to 61 patients; 36 per cent of these became pregnant. Of all patients who became pregnant 30 per cent received thyroid extract.

Tubal insufflation was done in 193 patients. A total of 306 such procedures was carried out. Hysterosalpingography was done 17 times. Tubal occlusion was diagnosed in 35 patients. The authors do not state how many of the pregnancies seem to be related to tubal studies.

Endometrial biopsies were studied in 135 patients. Normal ovarian function was diagnosed in 87 of these, endometrial hyperplasia in 24, endometrial hypoplasia in 11 and infection in 13. Single biopsies were done. Nine patients who failed to show ovulation at the time of the biopsy, eventually became pregnant. The authors do not state whether these pregnancies were in conjunction with therapy or not.—C.D.D.

REYNOLDS, S. R. M.: A spiral artery in the ovary of the rabbit, *Am. J. Obst. & Gynec.* **53**: 221–225 (Feb.) 1947.

A spiral artery within the hilus of the ovary of the rabbit is demonstrated. It is formed by a helix-type of formation from the ovarian artery as it enters the hilus of the ovary and turns sharply cephalad. Further vascularization of the ovary is accompanied by secondary branches arising from the coils of the spiral artery.

The author speculates as regards the implications of these findings. First, it may permit a "paying out" of the coils of the helix as growth of the ovary occurs. Second, a mechanism may be provided which allows for an orderly and progressive equalization of pressure within the ovary. Thirdly, alterations in this mechanism may be related to certain types of ovarian pathology whose etiology is now obscure.—C.D.D.

SCHMITZ, H., AND TOWNER, J. E: Radium and roentgen therapy in the treatment of menopausal uterine bleeding, *Am. J. Obst. & Gynec.* **53:** 199–206 (Feb.) 1947.

Of 412 patients who had functional climacteric uterine hemorrhage, 28.1 per cent received roentgen ray treatment and 71.8 per cent radium therapy. All had a preceding curettage. The roentgen ray dose was usually 500 roentgens and the radium dose, 1800 milligram hours. The duration of previous bleeding ranged from 1 to 36 months.

The clinical effects of the radiation therapy were as follows:

Menopausal manifestations	
mild or no symptoms	51.9 per cent
moderate	44.6
severe	3.8
Leukorrhea	
mild or none, 6 to 8 weeks after irradiation	76.6 per cent
moderate, 6 to 16 weeks after	22.8
prolonged, 20 or more weeks after	0.5
Cytitis (immediate—not prolonged)	3.6 per cent

Myomas occurred in 236 of these patients. The myomas were no larger than a three months' gestation and located intramurally. Only one patient was later subjected to subtotal hysterectomy for persistent pain attributed to a degeneration of the myoma. —C.D.D.

STURGIS, S. H.: Preliminary clinical report on a new synthetic estrogen, Meprane, *Am. J. Obst. & Gynec.:* **53:** 678–681 (April) 1947.

Meprane (34-Bis, M-methyl-propionoxy-phenyl, hexane) was evaluated in 34 patients who had been castrated 2 months to 9 years previously. Fifty-two courses of treatment, usually of 4 weeks' duration each, were given. The decrease in frequency of hot flushes was thought to be the best indicator of the effectiveness of a given dose. The usual dosage was 2 milligrams daily. Twenty-three of the patients obtained almost complete relief. Three patients were unable to tolerate the drug because of headache, vertigo and "tired feeling."

Moderate to marked vaginal cornification was produced by 2 to 3 milligrams of this drug daily.—C.D.D.

WILLIAMS, G. A., AND MENDENHALL, W. A.: Adrenal-like masculinizing tumor of the ovary associated with bleeding fibromyoma uteri, *Am. J. Obst. & Gynec.* **53:** 525–528 (March) 1947.

The authors present a case report of an adrenal-like tumor of the ovary in a 54-year-old woman. The presenting complaint was irregular vaginal bleeding of 36 months' duration. This was thought to be due to fibromyomata uteri. Virilism with acne and

hypertension were noted. Pathologic diagnosis was adrenal tumor of the ovary, multiple fibromyomata of the ovary with infarction of atrophic endometrium.—C.D.D.

PANCREAS

ELLENBERG, M., AND POLLACK, H.: Convulsive state in diabetes, *Am. J. M. Sc.* **214:** 503 (Nov.) 1947.

Two cases of labile diabetes associated with nonhypoglycemic reactions are described in order to shed some light on the unknown factors that underlie the unpredictability of sudden changes from glycosuria and ketonuria to convulsive states in these patients. Postmortem examination of the first case revealed definite pathologic changes justifying a diagnosis of: degenerative encephalopathy; toxic (?) encephalopathy. In the second case (patient still living) electroencephalograms showed alpha waves with frequencies as low as 7.5 per second with rare bursts of 6 per second activity and some single 3 per second waves.

The authors outline the following possibilities: 1) the pathologic findings in these patients are: the manifestations of irreversible cerebral changes following repeated insulin hypoglycemia; 2) the changes are independent of the diabetes and are actually an influence in the causation of repeated shocks; 3) they are evidences of coincidental epilepsy.

The most tenable assumption is that repeated severe insulin shocks produce irreversible cerebral damage.

The changes consist mainly of multiple petechial hemorrhages, proliferation of the glial tissue and widely disseminated injury to the nerve cells.

Therefore it is necessary to avoid hypoglycemic episodes in order to prevent their cumulative irreversible effects, and to be aware of the possibility of symptoms simulating shock resulting from causes other than hypoglycemia so that proper treatment may be instituted.—E.C.R.

HARTMANN, A. F., AND ERGANIAN, J.: Treatment of diabetic acidosis, *J. Pediat.* **31:** 274, 1947.

Since recognition and treatment of serious disturbances of acid base balance in infants and children constitute an important part of hospital pediatric practice, the authors draw on their long period of experience during which they encountered 1,465 instances of metabolic acidosis that were diagnosed by chemical determination of blood $BHCO_3$. They tabulate the incidence of metabolic acidosis, the calculation of alkali dosage, and the classification of severity of acidosis. They enumerate factors which either always operate or sometimes operate during recovery from severe acidemia and which would prevent administered Na-lactate or $NaHCO_3$ from appearing quantitatively as $BHCO_3$ in body fluids in a reasonably short time (6 to 12 hours), and also factors which would tend to supplement and enhance the effect of conversion of Na-lactate into $NaHCO_3$ in the tissue fluids, or increase the effect of administered $NaHCO_3$. The authors do not think it probable that any formula for calculation of an optimal dose of alkali for the relief of acidosis would work equally well for all cases. After enumerating the characteristics of severe acidosis, the authors list the objectives in the treatment of severe diabetic acidosis, and then analyze the results of treatment. Finally, they present an over-all summary of their results with the treatment of 123 children with diabetic acidosis with Na-lactate.—E.C.R.

HEARD, R. D. H.; LOZINSKI, E.; STEWART, L., AND STEWART, R. D.: An alpha cell hormone of the islets of Langerhans, *J. Biol. Chem.* **172:** 857–858, 1948.

Reports of a preliminary hyperglycemic action of relatively crude insulin preparations, recent recognition that the alpha cells exhibit the granulation characteristic of endocrine function, the effect of removal of the pancreas in the alloxan-diabetic dog, and various clinical data suggested that the alpha cells may produce a hormone which acts antagonistically to insulin. The supernatant solution from the first iso-electric precipitation in the preparation of crystalline zinc insulin was concentrated tenfold *in vacuo* and boiled 20 minutes at pH 9.5 to 9.7 in order to inactivate insulin.

Intraperitoneal injection of 2 ml. into rats resulted in hyperglycemia and loss of liver glycogen. Incubation of the extract with rat liver slices increased oxygen consumption and released 20 to 30 per cent more glucose than in treated controls.—H.L.M.

JACOBSON, P. H.: A statistical study of cancer among diabetics, *The Milbank Memorial Fund Quarterly, N. Y.* **26:** 90–118, 1948.

Critically analyzed statistical data demonstrate that the incidence of cancer is significantly greater among diabetics than among nondiabetics. This conclusion is substantiated by a comparison between the discrepancy in incidence of other diseases and cancer as compared with diabetes. It is stated that the data do not suggest any explanation for the positive association between diabetes and cancer.—R.H.

SEVRINGHAUS, E. L.: A psychomotor syndrome associated with a heterotopic pancreatic adenoma, *Psychosom. Med.* **2:** 109–110, 1948.

Demonstration of persistent fasting hypoglycemia led to two laparotomies before a heterotopic pancreatic adenoma was found and removed from a woman of 36 years, who had suffered from fatigue, persistent sleepiness, comatose attacks requiring glucose injection, and in whose encephalogram there was definite evidence of bilateral cortical atrophy. Recovery was symptomatically complete. Rorschach tests before and after operation showed distinct evidence of this reversal.—R.G.H.

GENERAL

BROWN, E. E., AND WASSON, V. P.: Capillary fragility and menses in rheumatic girls, *J. Pediat.* **30:** 455, 1947.

The authors discuss the duration and frequency of menses in 28 ambulant rheumatic girls and record capillary resistance in various phases of their menstrual cycle by the means of a modified Dalldorf resistometer, in order to determine the major factors influencing capillary resistance. The menstrual cycle was arbitrarily divided into three stages: 1) premenstrual—from the fourth day preceding menses to and including the first and second day of menses, 2) menstrual—from the third day to the end of menses, and 3) intermenstrual—from the end of menses to the fourth day prior to next menses. A table of capillary resistance readings in 28 rheumatic girls is given on the next page.

Bleeding phenomena in rheumatic girls are evidenced by an early menarche, prolongation of menses and shortening of the menstrual cycle. The bleeding tendency is increased during the premenstrual and menstrual phase, at which time there is a diminished capillary resistance amounting to 3 cm. of mercury suction. This capillary fragility is

	Rheumatic Girls	Average for American Girls
Age of menarche:	11.9 years	13½ years
Length of menses:	5.1 days	approximately 4 days
Menstrual cycle:	26.9 days	33.9 days
Capillary resistance:	Stage 1. 13.9 cm.	
	Stage 2. 14.4 cm.	
	Stage 3. 16.7 cm.	

presumably under glandular control. An even greater influence producing capillary fragility and menorrhagia in rheumatic girls is exerted by rheumatic toxin. The seasonal influence is also discussed.—E.C.R.

HIBBS, R.E.: Gynecomastia associated with vitamin deficiency disease, *Am. J. M. Sc.* **213**: 176, 1947.

The author presents observations on a group of American prisoners who were imprisoned from April 1942 to February 1945 in the Philippine Islands. During the 34 months of imprisonment of this group, malaria, dysentery and vitamin deficiency disease attacked almost every man in camp. Nutritional edema, pellagra, ariboflavinosis, beriberi, peripheral neuritis, scurvy, xerophthalmia and corneal ulceration had their onset in approximately that order between April and December 1942. An outbreak of gynecomastia was observed among the prisoners, and the first cases were seen in November 1943 or after one and one-half years of prison life, almost one year since the appearance of a new deficiency disease. During this period there was a relative increase in diet and a corresponding decrease in the evidence of malaria and dysentery. Ten per cent, i.e., 500, of the entire group of prisoners had breast disturbances. The onset of gynecomastia was insidious but simultaneous in this group. A small tumor appeared in both breasts. The maximum size of 2.5 to 3.5 cm. in diameter was reached in 2 to 3 months, and regression was complete in another 3 months. Improvement coincided with a shipment of Red Cross food and vitamins. A few cases showed a progressive enlargement of the breast after 6 months and these were surgically removed. Macroscopically these appeared to be small projections of tissue in the ducts. No facilities were available for microscopic examination. It is thought that the severe prolonged malnutrition had temporarily upset the endocrine balance, but there was no clinical evidence of degeneration of the liver which might have resulted in an excess of estrogen in the systemic circulation, nor was there any particular type of habitus among the involved men.—E.C.R.

INGALLS, T. H.: Pathogenesis of mongolism, *Am. J. Dis. Child.* **73**: 279, 1947.

The author presents pathologic evidence testing a hypothesis that whatever the cause of mongolism may be, the condition originates between the sixth and the ninth week of fetal life. He bases this evidence on the established features of the disorder supplemented by observations from the protocols of 50 autopsies performed during the past 25 years at the Children's Hospital in Boston. His enumeration of the established anatomic features of mongolism includes the following: skull; facies and nose; nasal bones, maxilla and palate; the eye; the ear; the brain; the skeleton; the heart and the blood vessels;

endocrine glands; and a few miscellaneous anomalies. The same listing is given in the composite report on observations at autopsy.

Mongolism then is interpreted as a variable syndrome made up of specific anomalies subject to numerous permutations. The final combination always includes brachycephaly and dwarfism of the basilar portion of the skull, the pathogenesis of which is discussed. The association of cranial with numerous skeletal anomalies suggests that developing masses of precartilage and membranous centers of ossification throughout the skeleton are affected in chance combinations. The involvement of the tribasilar bone may simply be one of them—the essential one for the production of the cranial stigmas, but of no etiologic significance.

The author recommends that attention be centered on the sixth to ninth weeks of fetal life in the search for possible etiologic agents, this being the period when the anomalies susceptible of embryologic orientation occur.—E.C.R.

KLATSKIN, G.; SALTER, W. T., AND HUMM, F. D.: Gynecomastia due to malnutrition. I. Clinical studies, *Am. J. M. Sc.* **213**: 19, 1947.

The authors' interest in the relationship between nutrition and the hormones and in the possible role of the liver led them to study 48 cases of gynecomastias associated with malnutrition. They report their clinical observations and the results of their investigation of the liver, but present their hormone excretion studies in a separate communication, *Am. J. M. Sci.* **213**: 31, 1947.

The patients were selected from a group of 300 American soldiers recently released from Japanese prison camps and transferred to an Army hospital for further study and treatment in December 1945.

Clinical investigation revealed abnormalities of the liver and genitalia. The relationship of these abnormalities to malnutrition and their possible role in the pathogenesis of gynecomastia is discussed at length in this report, but the findings did not warrant any definite conclusions regarding the pathogenesis of gynecomastia due to malnutrition.—E.C.R.

PAGE, E. W., AND OGDEN, E.: Endocrine influences upon the blood pressure of normal and hypertensive rats, *Am. J. Obst. & Gynec.* **53**: 150–154 (Jan.) 1947.

Remarkable constancy of blood pressure was found in all stages of the estrus cycle in 10 normal female rats. In 23 normal female rats the blood pressure showed a slight decline in the last quarter of pregnancy, and a rise of similar magnitude during lactation. After weaning, the pressure returned to a level somewhat below the original level.

Hypertension was induced by partial constriction of the left renal artery by means of a silk tie. Ten hypertensive rats were studied during the estrus cycle and no significant deviations were noted. Estrone, progesterone, chorionic gonadotropin and equine gonadotropin were given in varying doses to hypertensive rats and no consistent alteration in blood pressure was found.—C.D.D.

SALTER, W. T.; KLATSKIN, G., AND HUMM, F. D.: Gynecomastia due to malnutrition. II. Endocrine studies, *Am. J. M. Sc.* **213**: 31, 1947.

In the preceding report it was suggested that derangement of liver function may have contributed to the occurrence of gynecomastia due to malnutrition but the problem

seemed to the authors to be primarily one of endocrine imbalance, especially since testicular atrophy was noted. Therefore, in 27 patients, determinations of 17-ketosteroids, estrogens, "cortins," and follicle-stimulating hormone in the urine were made at a time when the subjects had returned to normal weight, and at intervals varying from one to 38 months after onset of gynecomastia. Control studies were made on normal individuals from military and civilian populations as well as cases of gynecomastia occurring in civilian life. The results showed that the patients with gynecomastia had lowered values for 17-ketosteroids, the estrogens were in the low normal range, "cortins" were normal, and no elevation of follicle-stimulating hormone was detected. The estrogen-androgen ratio was normal.

The authors conclude that their findings distinguish this group from gynecomastia of cirrhosis and acute hepatitis, but at the same time suggest that temporary derangement of liver function may play a prominent role in the pathogenesis of the lesion. They offer a possible alternative explanation that the pituitary-gonadal axis is primarily involved, and state that the group was not dissimilar to certain types of gynecomastia found in the civilian population.—E.C.R.